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(54) Title: ADENO-ASSOCIATED VIRUS SEROTYPE 1 NUCLEIC ACID SEQUENCES, VECTORS AND HOST CELLS CONTAINING SAME (57) Abstract The nucleic acid sequences of adeno-associated virus (AAV) serotype 1 are provided, as are vectors and host cells containing these sequences and functional fragments thereof. Also provided are methods of delivering genes via AAV-1 derived vectors.		

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ADENO-ASSOCIATED VIRUS SEROTYPE I NUCLEIC ACID SEQUENCES, VECTORS AND HOST CELLS CONTAINING SAME

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DK47757-06 and PO1 HD32649-04. The US government may have certain rights in
5 this invention.

Field of the Invention

This invention relates generally to viral vector, and more particularly, to
recombinant viral vectors useful for gene delivery.

Background of the Invention

10 Adeno-associated viruses are small, single-stranded DNA viruses which
require helper virus to facilitate efficient replication [K.I. Berns, *Parvoviridae: the
viruses and their replication*, p. 1007-1041, in F.N. Fields et al., Fundamental
virology, 3rd ed., vol. 2, (Lippencott-Raven Publishers, Philadelphia, PA) (1995)].
The 4.7 kb genome of AAV is characterized by two inverted terminal repeats (ITR)
15 and two open reading frames which encode the Rep proteins and Cap proteins,
respectively. The Rep reading frame encodes four proteins of molecular weight 78
kD, 68 kD, 52 kD and 40 kD. These proteins function mainly in regulating AAV
replication and integration of the AAV into a host cell's chromosomes. The Cap
reading frame encodes three structural proteins in molecular weight 85 kD (VP 1), 72
20 kD (VP2) and 61 kD (VP3) [Berns, cited above]. More than 80% of total proteins in
AAV virion comprise VP3. The two ITRs are the only cis elements essential for AAV
replication, packaging and integration. There are two conformations of AAV ITRs
called "flip" and "flop". These differences in conformation originated from the
replication model of adeno-associated virus which use the ITR to initiate and reinitiate
25 the replication [R.O. Snyder et al., J. Virol., 67:6096-6104 (1993); K.I. Berns,
Microbiological Reviews, 54:316-329 (1990)].

AAVs have been found in many animal species, including primates, canine,
fowl and human [F.A. Murphy et al., "The Classification and Nomenclature of
Viruses: Sixth Report of the International Committee on Taxonomy of Viruses",

Archives of Virology, (Springer-Verlag, Vienna) (1995)]. In addition to five known primate AAVs (AAV-1 to AAV-5), AAV-6, another serotype closely related to AAV-2 and AAV-1 has also been isolated [E. A. Rutledge et al., J. Virol., 72:309-319 (1998)]. Among all known AAV serotypes, AAV-2 is perhaps the most well-
5 characterized serotype, because its infectious clone was the first made [R.J. Samulski et al., Proc. Natl. Acad. Sci. USA, 79:2077-2081 (1982)]. Subsequently, the full sequences for AAV-3A, AAV-3B, AAV-4 and AAV-6 have also been determined [Rutledge, cited above; J.A. Chiorini et al., J. Virol., 71:6823-6833 (1997); S. Muramatsu et al., Virol., 221:208-217 (1996)]. Generally, all AAVs share more than
10 80% homology in nucleotide sequence.

A number of unique properties make AAV a promising vector for human gene therapy [Muzyczka, Current Topics in Microbiology and Immunology, 158:97-129 (1992)]. Unlike other viral vectors, AAVs have not been shown to be associated with any known human disease and are generally not considered pathogenic. Wild type
15 AAV is capable of integrating into host chromosomes in a site specific manner [R. M. Kotin et al., Proc. Natl. Acad. Sci. USA, 87:2211-2215 (1990)- R.J. Samulski, EMBO J., 10(12):3941-3950 (1991)]. Recombinant AAV vectors can integrate into tissue cultured cells in chromosome 19 if the rep proteins are supplied in *trans* [C. Balague et al., J. Virol., 71:3299-3306 (1997); R. T. Surosky et al., J. Virol.,
20 71:7951-7959 (1997)]. The integrated genomes of AAV have been shown to allow long term gene expression in a number of tissues, including, muscle, liver, and brain [K. J. Fisher, Nature Med., 3(3):306-312 (1997); R. O. Snyder et al., Nature Genetics, 16:270-276 (1997); X. Xiao et al., Experimental Neurology, 144:113-124 (1997); Xiao, J. Virol., 70(11):8098-8108 (1996)].

25 AAV-2 has been shown to be present in about 80-90% of the human population. Earlier studies showed that neutralizing antibodies for AAV-2 are prevalent [W. P. Parks et al., J. Virol., 2:716-722 (1970)]. The presence of such antibodies may significantly decrease the usefulness of AAV vectors based on AAV-2 despite its other merits. What are needed in the art are vectors characterized by the

advantages of AAV-2, including those described above, without the disadvantages, including the presence of neutralizing antibodies.

Summary of the Invention

In one aspect, the invention provides an isolated AAV-1 nucleic acid molecule
5 which is selected from among SEQ ID NO: 1, the strand complementary to SEQ ID NO: 1, and cDNA and RNA sequences complementary to SEQ ID NO: 1 and its complementary strand.

In another aspect, the present invention provides AAV ITR sequences, which include the 5' ITR sequences, nt 1 to 143 of SEQ ID NO: 1; the 3' ITR sequences, nt
10 4576 to 4718 of SEQ ID NO: 1, and fragments thereof.

In yet another aspect, the present invention provides a recombinant vector comprising an AAV-1 ITR and a selected transgene. Preferably, the vector comprises both the 5' and 3' AAV-1 ITRs between which the selected transgene is located.

In still another aspect, the invention provides a recombinant vector comprising
15 an AAV-1 P5 promoter having the sequence of nt 236 to 299 of SEQ ID NO: 1 or a functional fragment thereof.

In a further aspect, the present invention provides a nucleic acid molecule encoding an AAV-1 rep coding region and an AAV-1 cap coding region.

In still another aspect, the present invention provides a host cell transduced with a
20 recombinant viral vector of the invention. The invention further provides a host cell stably transduced with an AAV-1 P5 promoter of the invention.

In still a further aspect, the present invention provides a pharmaceutical composition comprising a carrier and a vector of the invention.

In yet another aspect, the present invention provides a method for AAV--
25 mediated delivery of a transgene to a host involving the step of delivering to a selected host a recombinant viral vector comprising a selected transgene under the control of sequences which direct expression thereof and an adeno-associated virus 1 (AAV-1) virion.

In another aspect, the invention provides a method for in vitro production of a selected gene product using a vector of the invention.

Other aspects and advantages of the invention will be readily apparent to one of skill in the art from the detailed description of the invention.

5 Brief Description of the Drawings

Figs. 1A-1C illustrate the alignment of nucleotides of AAV-1 [SEQ ID NO: 1], AAV-2 [SEQ ID NO: 18] and AAV-6 [SEQ ID NO: 19]. The alignment was done with MacVector 6.0. The full sequences of AAV-1 are shown in the top line. Nucleotides in AAV-2 and AAV-6 identical to AAV-1 are symbolized by "." and gaps by "-". Some of the conserved features among AAVs are marked in this figure. Note the 3' ITRs of AAV-1 and AAV-6 are shown in different orientations.

Fig. 2 illustrates the predicted secondary structure of AAV-1 ITR. The nucleotides in AAV-2 and AAV-6 are shown in italic and bold respectively.

Fig. 3A illustrates a hypothesis of how AAV-6 arose from the homologous recombination between AAV-1 and AAV-2. The major elements of AAV-1 are indicated in the graph. A region that is shared between AAV-1, AAV-2 and AAV-6 is shown in box with waved lines.

Fig. 3B is a detailed illustration of a 71 bp homologous region among AAV-1, AAV-2 and AAV-6. Nucleotides that differ among these serotypes are indicated by arrows.

Fig. 4A is a bar chart illustrating expression levels of human alpha 1 anti-trypsin ($\alpha 1$ AT) in serum following delivery of hAAT via recombinant AAV-1 and recombinant AAV-2 viruses.

Fig. 4B is a bar chart illustrating expression levels of erythropoietin (epo) in serum following delivery of the epo gene via recombinant AAV-1 and recombinant AAV-2 viruses.

Fig. 5A is a bar chart illustrating expression levels of $\alpha 1$ AT in liver following delivery of $\alpha 1$ AT as described in Example 7.

Fig. 5B is a bar chart demonstrating expression levels of epo in liver following delivery of epo as described in Example 7.

Fig. 5C is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-1 following delivery of α 1AT or epo to liver as described in Example 7.

5 Fig. 5D is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-2 following delivery of α 1AT or epo to liver as described in Example 7.

Fig. 6A is a bar chart illustrating expression levels of α 1AT in muscle following delivery of α 1AT as described in Example 7.

Fig. 6B is a bar chart demonstrating expression levels of epo in muscle
10 following delivery of epo as described in Example 7.

Fig. 6C is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-1 following delivery of α 1AT or epo to muscle as described in Example 7.

Fig. 6D is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-2 following delivery of α 1AT or epo to muscle as described in Example 7.

15 Detailed Description of the Invention

The present invention provides novel nucleic acid sequences for an adeno-- associated virus of serotype 1 (AAV-1). Also provided are fragments of these AAV-1 sequences. Among particularly desirable AAV-1 fragments are the inverted terminal repeat sequences (ITRs), rep and cap. Each of these fragments may be readily
20 utilized, e.g., as a cassette, in a variety of vector systems and host cells. Such fragments may be used alone, in combination with other AAV-1 sequences or fragments, or in combination with elements from other AAV or non-AAV viral sequences. In one particularly desirable embodiment, a cassette may contain the AAV-1 ITRs of the invention flanking a selected transgene. In another desirable
25 embodiment, a cassette may contain the AAV-1 rep and/or cap proteins, e.g., for use in producing recombinant (rAAV) virus.

Thus, the AAV-1 sequences and fragments thereof are useful in production of rAAV, and are also useful as antisense delivery vectors, gene therapy vectors, or vaccine vectors. The invention further provides nucleic acid molecules, gene delivery

vectors, and host cells which contain the AAV-1 sequences of the invention. Also provided a novel methods of gene delivery using AAV vectors.

As described herein, the vectors of the invention containing the AAV-1 capsid proteins of the invention are particularly well suited for use in applications in which the neutralizing antibodies diminish the effectiveness of other AAV serotype based vectors, as well as other viral vectors. The rAAV vectors of the invention are particularly advantageous in rAAV readministration and repeat gene therapy.

These and other embodiments and advantages of the invention are described in more detail below. As used throughout this specification and the claims, the term “comprising” is inclusive of other components, elements, integers, steps and the like.

I. AAV-1 NUCLEIC ACID AND PROTEIN SEQUENCES

The AAV-1 nucleic acid sequences of the invention include the DNA sequences of SEQ ID NO: 1 (Figs. 1A-1C), which consists of 4718 nucleotides. The AAV-1 nucleic acid sequences of the invention further encompass the strand which is complementary to SEQ ID NO: 1, as well as the RNA and cDNA sequences corresponding to SEQ ID NO: 1 and its complementary strand. Also included in the nucleic acid sequences of the invention are natural variants and engineered modifications of SEQ ID NO: 1 and its complementary strand. Such modifications include, for example, labels which are known in the art, methylation, and substitution of one or more of the naturally occurring nucleotides with an analog.

Further included in this invention are nucleic acid sequences which are greater than 85%, preferably at least about 90%, more preferably at least about 95%, and most preferably at least about 98 - 99% identical or homologous to SEQ ID NO: 1. The term “percent sequence identity” or “identical” in the context of nucleic acid sequences refers to the residues in the two sequences which are the same when aligned for maximum correspondence. The length of sequence identity comparison may be over the full-length sequence, or a fragment at least about nine nucleotides, usually at least about 20 - 24 nucleotides, at least about 28 - 32 nucleotides, and preferably at least about 36 or more nucleotides. There are a number of different

algorithms known in the art which can be used to measure nucleotide sequence identity. For instance, polynucleotide sequences can be compared using Fasta, a program in GCG Version 6.1. Fasta provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences
5 (Pearson, 1990, herein incorporated by reference). For instance, percent sequence identity between nucleic acid sequences can be determined using Fasta with its default parameters (a word size of 6 and the NOPAM factor for the scoring matrix) as provided in GCG Version 6.1, herein incorporated by reference.

The term "substantial homology" or "substantial similarity," when referring to
10 a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 95 - 99% of the sequence.

Also included within the invention are fragments of SEQ ID NO: 1, its
15 complementary strand, cDNA and RNA complementary thereto. Suitable fragments are at least 15 nucleotides in length, and encompass functional fragments which are of biological interest. Certain of these fragments may be identified by reference to Figs. 1A-1C. Examples of particularly desirable functional fragments include the AAV-1 inverted terminal repeat (ITR) sequences of the invention. In contrast to the 145 nt
20 ITRs of AAV-2, AAV-3, and AAV-4, the AAV-1 ITRs have been found to consist of only 143 nucleotides, yet advantageously are characterized by the T-shaped hairpin structure which is believed to be responsible for the ability of the AAV-2 ITRs to direct site-specific integration. In addition, AAV-1 is unique among other AAV serotypes, in that the 5' and 3' ITRs are identical. The full-length 5' ITR sequences of
25 AAV-1 are provided at nucleotides 1-143 of SEQ ID NO: 1 (Fig. 1A) and the full-length 3' ITR sequences of AAV-1 are provided at nt 4576-4718 of SEQ ID NO: 1 (Fig. 1C). One of skill in the art can readily utilize less than the full-length 5' and/or 3' ITR sequences for various purposes and may construct modified ITRs using conventional techniques, e.g., as described for AAV-2 ITRs in Samulski et al, Cell,
30 33:135-143 (1983).

Another desirable functional fragment of the AAV-1 genome is the P5 promoter of AAV-1 which has sequences unique among AAV P5 promoters, while maintaining critical regulatory elements and functions. This promoter is located within nt 236 - 299 of SEQ ID NO: 1 (Fig. 1A). Other examples of functional fragments of interest include the sequences at the junction of the rep/cap, e.g., the sequences spanning nt 2306-2223, as well as larger fragments which encompass this junction which may comprise 50 nucleotides on either side of this junction. Still other examples of functional fragments include the sequences encoding the rep proteins. Rep 78 is located in the region of nt 334 - 2306 of SEQ ID NO: 1; Rep 68 is located in the region of nt 334-2272, and contains an intron spanning nt 1924-2220 of SEQ ID NO: 1. Rep 52 is located in the region of nt 1007 - 2304 of SEQ ID NO: 1; rep 40 is located in the region of nt 1007 - 2272, and contains an intron spanning nt 1924-2246 of SEQ ID NO: 1. Also of interest are the sequences encoding the capsid proteins, VP 1 [nt 2223-4431 of SEQ ID NO: 1], VP2 [nt 2634-4432 of SEQ ID NO: 1] and VP3 [nt 2829-4432 of SEQ ID NO: 1]. Other fragments of interest may include the AAV-1 P19 sequences, AAV-1 P40 sequences, the rep binding site, and the terminal resolute site (TRS).

The invention further provides the proteins and fragments thereof which are encoded by the AAV-1 nucleic acids of the invention. Particularly desirable proteins include the rep and cap proteins, which are encoded by the nucleotide sequences identified above. These proteins include rep 78 [SEQ ID NO:5], rep 68 [SEQ ID NO:7], rep 52 [SEQ ID NO:9], rep 40 [SEQ ID NO: 11], vpl [SEQ ID NO: 13], vp2 [SEQ ID NO: 15], and vp3 [SEQ IID NO: 17] and functional fragments thereof while the sequences of the rep and cap proteins have been found to be closely related to those of AAV-6, there are differences in the amino acid sequences (see Table 1 below), as well as differences in the recognition of these proteins by the immune system. However, one of skill in the art may readily select other suitable proteins or protein fragments of biological interest. Suitably, such fragments are at least 8 amino acids in length. However, fragments of other desired lengths may be readily utilized.

Such fragments may be produced recombinantly or by other suitable means, e.g., chemical synthesis.

The sequences, proteins, and fragments of the invention may be produced by any suitable means, including recombinant production, chemical synthesis, or other synthetic means. Such production methods are within the knowledge of those of skill in the art and are not a limitation of the present invention.

II. VIRAL VECTORS

In another aspect, the present invention provides vectors which utilize the AAV-1 sequences of the invention, including fragments thereof, for delivery of a heterologous gene or other nucleic acid sequences to a target cell. Suitably, these heterologous sequences (i.e., a transgene) encode a protein or gene product which is capable of being expressed in the target cell. Such a transgene may be constructed in the form of a "minigene". Such a "minigene" includes selected heterologous gene sequences and the other regulatory elements necessary to transcribe the gene and express the gene product in a host cell. Thus, the gene sequences are operatively linked to regulatory components in a manner which permit their transcription. Such components include conventional regulatory elements necessary to drive expression of the transgene in a cell containing the viral vector. The minigene may also contain a selected promoter which is linked to the transgene and located, with other regulatory elements, within the selected viral sequences of the recombinant vector.

Selection of the promoter is a routine matter and is not a limitation of this invention. Useful promoters may be constitutive promoters or regulated (inducible) promoters, which will enable control of the timing and amount of the transgene to be expressed. For example, desirable promoters include the cytomegalovirus (CMV) immediate early promoter/enhancer [see, e.g., Boshart et al, Cell, 41:521-530 (1985)], the Rous sarcoma virus LTR promoter/enhancer, and the chicken cytoplasmic β -actin promoter [T. A. Kost et al, Nucl. Acids Res., 11(23):8287 (1983)]. Still other desirable promoters are the albumin promoter and an AAV P5 promoter. Optionally, the selected promoter is used in conjunction with a heterologous enhancer, e.g., the β -

actin promoter may be used in conjunction with the CMV enhancer. Yet other suitable or desirable promoters and enhancers may be selected by one of skill in the art.

The minigene may also desirably contain nucleic acid sequences heterologous to the viral vector sequences including sequences providing signals required for efficient polyadenylation of the transcript (poly-A or pA) and introns with functional splice donor and acceptor sites. A common poly-A sequence which is employed in the exemplary vectors of this invention is that derived from the papovavirus SV-40. The poly-A sequence generally is inserted in the minigene downstream of the transgene sequences and upstream of the viral vector sequences. A common intron sequence is also derived from SV-40, and is referred to as the SV40 T intron sequence. A minigene of the present invention may also contain such an intron, desirably located between the promoter/enhancer sequence and the transgene. Selection of these and other common vector elements are conventional [see, e.g., Sambrook et al, "Molecular Cloning. A Laboratory Manual", 2d edit., Cold Spring Harbor Laboratory, New York (1989) and references cited therein] and many such sequences are available from commercial and industrial sources as well as from Genebank.

The selection of the transgene is not a limitation of the present invention. Suitable transgenes may be readily selected from among desirable reporter genes, therapeutic genes, and optionally, genes encoding immunogenic polypeptides. Examples of suitable reporter genes include β -galactosidase (β -gal), an alkaline phosphatase gene, and green fluorescent protein (GFP). Examples of therapeutic genes include, cytokines, growth factors, hormones, and differentiation factors, among others. The transgene may be readily selected by one of skill in the art. See, e.g., WO 98/09657, which identifies other suitable transgenes.

Suitably, the vectors of the invention contain, at a minimum, cassettes which consist of fragments of the AAV-1 sequences and proteins. In one embodiment, a vector of the invention comprises a selected transgene, which is flanked by a 5' ITR and a 3' ITR, at least one of which is an AAV-1 ITR of the invention. Suitably,

vectors of the invention may contain a AAV-1 P5 promoter of the invention. In yet another embodiment, a plasmid or vector of the invention contains AAV-1 rep sequences. In still another embodiment, a plasmid or vector of the invention contains at least one of the AAV-1 cap proteins of the invention. Most suitably, these AAV-1-derived vectors are assembled into viral vectors, as described herein.

A. AAV Viral Vectors

In one aspect, the present invention provides a recombinant AAV-1 viral vector produced using the AAV-1 capsid proteins of the invention. The packaged rAAV-1 virions of the invention may contain, in addition to a selected minigene, other AAV-1 sequences, or may contain sequences from other AAV serotypes.

Methods of generating rAAV virions are well known and the selection of a suitable method is not a limitation on the present invention. See, e.g., K. Fisher et al, J. Virol., 70:520-532 (1993) and US Patent 5,478,745. In one suitable method, a selected host cell is provided with the AAV sequence encoding a rep protein, the gene encoding the AAV cap protein and with the sequences for packaging and subsequent delivery. Desirably, the method utilizes the sequences encoding the AAV-1 rep and/or cap proteins of the invention.

In one embodiment, the rep/cap genes and the sequences for delivery are supplied by co-transfection of vectors carrying these genes and sequences. In one currently preferred embodiment, a cis (vector) plasmid, a trans plasmid containing the rep and cap genes, and a plasmid containing the adenovirus helper genes are co-transfected into a suitable cell line, e.g., 293. Alternatively, one or more of these functions may be provided in trans via separate vectors, or may be found in a suitably engineered packaging cell line.

An exemplary cis plasmid will contain, in 5' to 3' order, AAV 5' ITR, the selected transgene, and AAV 3' ITR. In one desirable embodiment, at least one of the AAV ITRs is a 143 nt AAV-1 ITR. However, other AAV serotype ITRs may be readily selected. Suitably, the full-length ITRs are utilized. However, one of skill in

the art can readily prepare modified AAV ITRs using conventional techniques. Similarly, methods for construction of such plasmids is well known to those of skill in the art.

A trans plasmid for use in the production of the rAAV-1 virion particle
5 may be prepared according to known techniques. In one desired embodiment, this plasmid contains the rep and cap proteins of AAV-1, or functional fragments thereof. Alternatively, the rep sequences may be from another selected AAV serotype.

The cis and trans plasmid may then be co-transfected with a wild-type
helper virus (e.g., Ad2, Ad5, or a herpesvirus), or more desirably, a replication -
10 defective adenovirus, into a selected host cell. Alternatively, the cis and trans plasmid may be co-transfected into a selected host cell together with a transfected plasmid which provides the necessary helper functions. Selection of a suitable host cell is well within the skill of those in the art and include such mammalian cells as 293 cells, HeLa cells, among others.

15 Alternatively, the cis plasmid and, optionally the trans plasmid, may be transfected into a packaging cell line which provides the remaining helper functions necessary for production of a rAAV containing the desired AAV-1 sequences of the invention. An example of a suitable packaging cell line, where an AAV-2 capsid is desired, is B-50, which stably expresses AAV-2 rep and cap genes under the control
20 of a homologous P5 promoter. This cell line is characterized by integration into the cellular chromosome of multiple copies (at least 5 copies) of P5-rep-cap gene cassettes in a concatomer form. This B-50 cell line was deposited with the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209, on September 18, 1997 under Accession No. CRL-12401 pursuant to the
25 provisions of the Budapest Treaty. However, the present invention is not limited as to the selection of the packaging cell line.

Exemplary transducing vectors based on AAV-1 capsid proteins have been tested both *in vivo* and *in vitro*, as described in more detail in Example 4. In these studies, it was demonstrated that recombinant AAV vector with an AAV-1
30 virion can transduce both mouse liver and muscle. These, and other AAV-1 based

gene therapy vectors which may be generated by one of skill in the art are beneficial for gene delivery to selected host cells and gene therapy patients since the neutralization antibodies of AAV-1 present in much of the human population exhibit different patterns from other AAV serotypes and therefore do not neutralize the AAV-1 virions. One of skill in the art may readily prepare other rAAV viral vectors containing the AAV-1 capsid proteins provided herein using a variety of techniques known to those of skill in the art. One may similarly prepare still other rAAV viral vectors containing AAV-1 sequence and AAV capsids of another serotype.

B. Other Viral Vectors

One of skill in the art will readily understand that the AAV-1 sequences of the invention can be readily adapted for use in these and other viral vector systems for *in vitro*, *ex vivo* or *in vivo* gene delivery. Particularly well suited for use in such viral vector systems are the AAV-1 ITR sequences, the AAV-1 rep, the AAV-1 cap, and the AAV-1 P5 promoter sequences.

For example, in one desirable embodiment, the AAV-1 ITR sequences of the invention may be used in an expression cassette which includes AAV-1 5' ITR, a non-AAV DNA sequences of interest (e.g., a minigene), and 3' ITR and which lacks functional rep/cap. Such a cassette containing an AAV-1 ITR may be located on a plasmid for subsequent transfection into a desired host cell, such as the cis plasmid described above. This expression cassette may further be provided with an AAV capsid of a selected serotype to permit infection of a cell or stably transfected into a desired host cell for packaging of rAAV virions. Such an expression cassette may be readily adapted for use in other viral systems, including adenovirus systems and lentivirus systems. Methods of producing Ad/AAV vectors are well known to those of skill in the art. One desirable method is described in PCT/US95/14018. However, the present invention is not limited to any particular method.

Another aspect of the present invention is the novel AAV-1 P5 promoter sequences which are located in the region spanning nt 236 - 299 of SEQ ID NO: 1. This promoter is useful in a variety of viral vectors for driving expression of a desired transgene.

Similarly, one of skill in the art can readily select other fragments of the AAV-1 genome of the invention for use in a variety of vector systems. Such vector systems may include, e.g., lentiviruses, retroviruses, poxviruses, vaccinia viruses, and adenoviral systems, among others. Selection of these vector systems is not a
5 limitation of the present invention.

C. Host Cells And Packaging Cell Lines

In yet another aspect, the present invention provides host cells which may be transiently transfected with AAV-1 nucleic acid sequences of the invention to permit expression of a desired transgene or production of a rAAV particle. For
10 example, a selected host cell may be transfected with the AAV-1 P5 promoter sequences and/or the AAV-1 5' ITR sequences using conventional techniques. Providing AAV helper functions to the transfected cell lines of the invention results in packaging of the rAAV as infectious rAAV particles. Such cell lines may be produced in accordance with known techniques [see, e.g., US Patent No. 5,658,785], making
15 use of the AAV-1 sequences of the invention.

Alternatively, host cells of the invention may be stably transfected with a rAAV expression cassette of the invention, and with copies of AAV-1 rep and cap genes. Suitable parental cell lines include mammalian cell lines and it may be desirable to select host cells from among non-simian mammalian cells. Examples of suitable
20 parental cell lines include, without limitation, HeLa [ATCC CCL 2], A549 [ATCC Accession No. CCL 185], KB [CCL 17], Detroit [e.g., Detroit 510, CCL 72] and WI-38 [CCL 75] cells. These cell lines are all available from the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209 USA. Other suitable parent cell lines may be obtained from other sources and may be used to
25 construct stable cell lines containing the P5 and/or AAV rep and cap sequences of the invention.

Recombinant vectors generated as described above are useful for delivery of the DNA of interest to cells.

III. METHODS OF DELIVERING GENES VIA AAV-1 DERIVED VECTORS

In another aspect, the present invention provides a method for delivery of a transgene to a host which involves transfecting or infecting a selected host cell with a recombinant viral vector generated with the AAV-1 sequences (or functional
5 fragments thereof) of the invention. Methods for delivery are well known to those of skill in the art and are not a limitation of the present invention.

In one desirable embodiment, the invention provides a method for AAV--mediated delivery of a transgene to a host. This method involves transfecting or infecting a selected host cell with a recombinant viral vector containing a selected
10 transgene under the control of sequences which direct expression thereof and AAV-1 capsid proteins.

Optionally, a sample from the host may be first assayed for the presence of antibodies to a selected AAV serotype. A variety of assay formats for detecting neutralizing antibodies are well known to those of skill in the art. The selection of
15 such an assay is not a limitation of the present invention. See, e.g., Fisher et al, Nature Med., 3(3):306-312 (March 1997) and W. C. Manning et al, Human Gene Therapy, 9:477-485 (March 1, 1998). The results of this assay may be used to determine which AAV vector containing capsid proteins of a particular serotype are preferred for delivery, e.g., by the absence of neutralizing antibodies specific for that
20 capsid serotype.

In one aspect of this method, the delivery of vector with AAV-1 capsid proteins may precede or follow delivery of a gene via a vector with a different serotype AAV capsid protein. Thus, gene delivery via rAAV vectors may be used for repeat gene delivery to a selected host cell. Desirably, subsequently administered
25 rAAV vectors carry the same transgene as the first rAAV vector, but the subsequently administered vectors contain capsid proteins of serotypes which differ from the first vector. For example, if a first vector has AAV-2 capsid proteins, subsequently administered vectors may have capsid proteins selected from among the other serotypes, including AAV-1, AAV-3A, AAV-3B, AAV-4 and AAV-6.

Thus, a rAAV-1-derived recombinant viral vector of the invention provides an efficient gene transfer vehicle which can deliver a selected transgene to a selected host cell *in vivo or ex vivo* even where the organism has neutralizing antibodies to one or more AAV serotypes. These compositions are particularly well suited to gene
5 delivery for therapeutic purposes. However, the compositions of the invention may also be useful in immunization. Further, the compositions of the invention may also be used for production of a desired gene product *in vitro*.

The above-described recombinant vectors may be delivered to host cells according to published methods. An AAV viral vector bearing the selected transgene
10 may be administered to a patient, preferably suspended in a biologically compatible solution or pharmaceutically acceptable delivery vehicle. A suitable vehicle includes sterile saline. Other aqueous and non-aqueous isotonic sterile injection solutions and aqueous and non-aqueous sterile suspensions known to be pharmaceutically acceptable carriers and well known to those of skill in the art may be employed for
15 this purpose.

The viral vectors are administered in sufficient amounts to transfect the cells and to provide sufficient levels of gene transfer and expression to provide a therapeutic benefit without undue adverse effects, or with medically acceptable physiological effects, which can be determined by those skilled in the medical arts.
20 Conventional and pharmaceutically acceptable routes of administration include, but are not limited to, direct delivery to the liver, oral, intranasal, intravenous, intramuscular, subcutaneous, intradermal, and other parental routes of administration. Routes of administration may be combined, if desired.

Dosages of the viral vector will depend primarily on factors such as the
25 condition being treated, the age, weight and health of the patient, and may thus vary among patients. For example, a therapeutically effective human dosage of the viral vector is generally in the range of from about 1 ml to about 100 ml of solution containing concentrations of from about 1×10^9 to 1×10^{16} genomes virus vector. A preferred human dosage may be about 1×10^{13} to 1×10^{16} AAV genomes. The
30 dosage will be adjusted to balance the therapeutic benefit against any side effects and

such dosages may vary depending upon the therapeutic application for which the recombinant vector is employed. The levels of expression of the transgene can be monitored to determine the frequency of dosage resulting in viral vectors, preferably AAV vectors containing the minigene. Optionally, dosage regimens similar to those described for therapeutic purposes may be utilized for immunization using the compositions of the invention. For *in vitro* production, a desired protein may be obtained from a desired culture following transfection of host cells with a rAAV containing the gene encoding the desired protein and culturing the cell culture under conditions which permits expression. The expressed protein may then be purified and isolated, as desired. Suitable techniques for transfection, cell culturing, purification, and isolation are known to those of skill in the art.

The following examples illustrate several aspects and embodiments of the invention.

Example 1 - Generation of Infectious Clone of AAV-1

The replicated form DNA of AAV-1 was extracted from 293 cells that were infected by AAV-1 and wild type adenovirus type 5.

A. Cell Culture and Virus

AAV-free 293 cells and 84-31 cells were provided by the human application laboratory of the University of Pennsylvania. These cells were cultured in Dulbecco's Modified Eagle Medium with 10% fetal bovine serum (Hyclone), penicillin (100 U/ml) and streptomycin at 37°C in a moisturized environment supplied with 5% CO₂. The 84-31 cell line constitutively expresses adenovirus genes E1a, E1b, E4/ORF6, and has been described previously [K. J. Fisher, *J. Virol.*, 70:520-532 (1996)]. AAV-1 (ATCC VR-645) seed stock was purchased from American Type Culture Collection (ATCC, Manassas, VA). AAV viruses were propagated in 293 cells with wild type Ad5 as a helper virus.

B. Recombinant AAV Generation

The recombinant AAV viruses were generated by transfection using an adenovirus free method. Briefly, the cis plasmid (with AAV ITR), trans plasmid (with

AAV rep gene and cap gene) and helper plasmid (pF Δ 13, with essential regions from the adenovirus genome) were simultaneously co-transfected into 293 cells in a ratio of 1:1:2 by calcium phosphate precipitation. The pF Δ 13 helper plasmid has an 8 kb deletion in the adenovirus E2B region and has deletions in most of the late genes.

5 This helper plasmid was generated by deleting the RsrII fragment from pFG140 (Microbix, Canada). Typically, 50 μ g of DNA (cis:trans:PF Δ 13 at ratios of 1:1:2, respectively) was transfected onto a 15 cm tissue culture dish. The cells were harvested 96 hours post-transfection, sonicated and treated with 0.5% sodium deoxycholate (37°C for 10 min). Cell lysates were then subjected to two rounds of a

10 CsCl gradient. Peak fractions containing AAV vector were collected, pooled, and dialyzed against PBS before injecting into animals. To make rAAV virus with AAV-1 virion, the pAV1H or p5E18 (2/1) was used as the *trans* plasmid to provide rep and cap function.

For the generation of rAAV based on AAV-2, p5E18 was used as the

15 *trans* plasmid since it greatly improved the rAAV yield. This plasmid, p5E18(2/2), expresses AAV-2 Rep and Cap and contains a P5 promoter relocated to a position 3' to the Cap gene, thereby minimizing expression of Rep78 and Rep68. The strategy was initially described by Li et al, *J. Virol.*, 71:5236-5243 (1997). P5E18(2/2) was constructed in the following way. The previously described pMMTV-*trans* vector

20 (i.e., the mouse mammary tumor virus promoter substituted for the P5 promoter in an AAV-2-based vector) was digested with *Sma*I and *Cla*I, filled in with the Klenow enzyme, and then recircularized with DNA ligase. The resulting construct was digested with *Xba*I, filled in, and ligated to the blunt-ended BamHI-*Xba*I fragment from pCR-p5, constructed in the following way. The P5 promoter of AAV was

25 amplified by PCR and the amplified fragment was subsequently cloned into pCR2.1 (Invitrogen) to yield pCR-P5. The helper plasmid pAV1H was constructed by cloning the *Bfa*I fragment of pAAV-2 into pBluescript II-SK(+) at the *Bco*rV and *Sma*I sites. The 3.0-kb *Xba*I-*Kpn*I fragment from p5E18(2/2), the 2.3-kb *Xba*I-*Kpn*I fragment from pAV1H, and the 1.7-kb *Kpn*I fragment from p5E18(2/2) were incorporated into

30 a separate plasmid P5E18(2/1), which contains AAV-2 Rep, AAV-1 Cap, and the

AAV-2 P5 promoter located 3' to the Cap gene. Plasmid p5E18(2/1) produced 10- to 20-fold higher quantities of the vector than pAV1H (i.e., 10^{12} genomes/50 15-cm² plates).

C. DNA Techniques

5 Hirt DNA extraction was performed as described in the art with minor modification [R.J. Samulski et al., Cell, 33:135-143 (1983)]. More particularly, Hirt solution without SDS was used instead of using original Hirt solution containing SDS. The amount of SDS present in the original Hirt solution was added after the cells had been fully suspended. To construct AAV-1 infectious clone, the Hirt DNA from
10 AAV-1 infected 293 cells was repaired with Klenow enzyme (New England Biolabs) to ensure the ends were blunt. The treated AAV-1 Hirt DNA was then digested with *Bam*HI and cloned into three vectors, respectively. The internal *Bam*HI was cloned into pBlueScript II-SK+ cut with *Bam*HI to get pAV1-BM. The left and right fragments were cloned into pBlueScript II-SK+ cut with *Bam*HI + EcoRV to obtain
15 pAV1-BL and pAV1-BR, respectively. The AAV sequence in these three plasmids were subsequently assembled into the same vector to get AAV-1 infectious clone pAAV-1. The helper plasmid for recombinant AAV-1 virus generation was constructed by cloning the Bfa I fragment of pAAV-1 into pBlueScript II-SK+ at the EcoRV site.
20 Analysis of the Hirt DNA revealed three bands, a dimer at 9.4 kb, a monomer at 4.7 kb and single-stranded DNA at 1.7 kb, which correlated to different replication forms of AAV-1. The monomer band was excised from the gel and then digested with *Bam*HI. This resulted in three fragments of 1.1 kb, 0.8 kb and 2.8 kb. This pattern is in accordance with the description by Bantel-schaal and zur Hausen,
25 Virol., 134(1):52-63 (1984). The 1.1 kb and 2.8 kb *Bam*HI fragments were cloned into pBlueScript-KS(+) at *Bam*HI and EcoRV site. The internal 0.8 kb fragment was cloned into *Bam*HI site of pBlueScript-KS(+).

 These three fragments were then subcloned into the same construct to obtain a plasmid (pAAV-1) that contained the full sequence of AAV-1. The pAAV-1
30 was then tested for its ability to rescue from the plasmid backbone and package

infectious virus. The pAAV-1 was then transfected to 293 cells and supplied with adenovirus type as helper at MOI 10. The virus supernatant was used to reinfect 293 cells.

For Southern blot analysis, Hirt DNA was digested with *DpnI* to
5 remove bacteria-borne plasmid and probed with internal *BamHI* fragment of AAV-1. The membrane was then washed at high stringency conditions, which included: twice 30 minutes with 2X SSC, 0.1% SDS at 65°C and twice 30 minutes with 0.1X SSC, 0.1% SDS at 65°C. The membrane was then analyzed by both phosphor image and X-ray autoradiography. The results confirmed that pAAV-1 is indeed an infectious
10 clone of AAV serotype 1.

Example 2 - Sequencing Analysis of AAV-1

The entire AAV-1 genome was then determined by automatic sequencing and was found to be 4718 nucleotides in length (Figs. 1A-1C). For sequencing, an ABI 373 automatic sequencer as used to determine the sequences for all plasmids and PCR
15 fragments related to this study using the FS dye chemistry. All sequences were confirmed by sequencing both plus and minus strands. These sequences were also confirmed by sequencing two independent clones of pAV-BM, pAV-BL and pAV-BR. Since the replicated form of AAV-1 DNA served as the template for sequence determination, these sequences were also confirmed by sequencing a series of PCR
20 products using original AAV-1 seed stock as a template.

The length of AAV-1 was found to be within the range of the other serotypes: AAV-3 (4726 nucleotides), AAV-4 (4774 nucleotides), AAV-2 (4681 nucleotides), and AAV-6 (4683 nucleotides).

The AAV-1 genome exhibited similarities to other serotypes of adeno-
25 associated viruses. Overall, it shares more than 80% identity with other known AAV viruses as determined by the computer program Megalign using default settings [DNASTAR, Madison, WI]. The key features in AAV-2 can also be found in AAV-1. First, AAV-1 has the same type of inverted terminal repeat which is capable of forming T-shaped hairpin structures, despite the differences at the nucleotide level

(Figs. 2 and 3). The sequences of right ITRs and left ITRs of AAV-1 are identical. The AAV TR sequence is subdivided into A, A', B, B', C, C', D and D' [Bern, cited above].

These AAV ITR sequences are also virtually the same as those found in AAV-6 right ITR, there being one nucleotide difference in each of A and A' sequence, and the last nucleotide of the D sequence. Second, the AAV-2 rep binding motif [GCTCGCTCGCTCGCTG (SEQ ID NO: 20)] is well conserved. Such motif can also be found in the human chromosome 19 AAV-2 pre-integration region. Finally, non-structural and structural coding regions, and regulatory elements similar to those of other AAV serotypes also exist in AAV-1 genome.

Although the overall features of AAV terminal repeats are very much conserved, the total length of the AAV terminal repeat exhibits divergence. The terminal repeat of AAV-1 consists of 143 nucleotides while those of AAV-2, AAV-3, and AAV-4 are about 145 or 146 nucleotides. The loop region of AAV-1 ITR most closely resembles that of AAV-4 in that it also uses TCT instead of the TTT found in AAV-2 and AAV-3. The possibility of sequencing error was eliminated using restriction enzyme digestion, since these three nucleotides are part of the SacI site (gagctc; nt 69-74 of SEQ ID NO: 1). The p5 promoter region of AAV-1 shows more variations in nucleotide sequences with other AAV serotypes. However, it still maintains the critical regulatory elements. The two copies of YY1 [See, Fig. 1A-1C] sites seemed to be preserved in all known AAV serotypes, which have been shown to be involved in regulating AAV gene expression. In AAV-4, there are 56 additional nucleotides inserted between YY1 and E-box/USF site, while in AAV-1, there are 26 additional nucleotides inserted before the E-box/USF site. The p19 promoter, p40 promoter and polyA can also be identified from the AAV-1 genome by analogy to known AAV serotypes, which are also highly conserved.

Thus, the analysis of AAV terminal repeats of various serotypes showed that the A and A' sequence is very much conserved. One of the reasons may be the Rep binding motif (GCTC)₂GCTG [SEQ ID NO: 20]. These sequences appear to be essential for AAV DNA replication and site-specific integration. The same sequence

has also been shown to be preserved in a monkey genome [Samulski, personal communication]. The first 8 nucleotides of the D sequence are also identical in all known AAV serotypes. This is in accordance with the observation of the Srivastava group that only the first 10 nucleotides are essential for AAV packaging [X.S. Wang et al, *J. Virol.*, 71:3077-3082 (1997); X.S. Wang et al, *J. Virol.*, 71:1140-1146 (1997)]. The function of the rest of the D sequences still remain unclear. They may be somehow related to their tissue specificities. The variation of nucleotide in B and C sequence may also suggest that the secondary structure of the ITRs is more critical for its biological function, which has been demonstrated in many previous publications.

Example 3 - Comparison of AAV-1 Sequences

The nucleotide sequences of AAV-1, obtained as described above, were compared with known AAV sequences, including AAV-2, AAV-4 and AAV-6 using DNA Star Megalign. This comparison revealed a stretch of 71 identical nucleotides shared by AAV-1, AAV-2 and AAV-6. See, Figs. 1A-1C.

This comparison further suggested that AAV-6 is a hybrid formed by homologous recombination of AAV-1 and AAV-2. See, Figs. 3A and 3B. These nucleotides divide the AAV-6 genome into two regions. The 5' half of AAV-6 of 522 nucleotides is identical to that of AAV-2 except in 2 positions. The 3' half of AAV-6 including the majority of the rep gene, complete cap gene and 3' ITR is 98% identical to AAV-1.

Biologically, such recombination may enable AAV-1 to acquire the ability to transmit through the human population. It is also interesting to note that the ITRs of AAV-6 comprise one AAV-1 ITR and one AAV-2 ITR. The replication model of defective parvovirus can maintain this special arrangement. Studies on AAV integration have shown that a majority of AAV integrants carries deletions in at least one of the terminal repeats. These deletions have been shown to be able to be repaired through gene conversion using the other intact terminal repeat as a template. Therefore, it would be very difficult to maintain AAV-6 as a homogenous population

when an integrated copy of AAV-6 is rescued from host cells with helper virus infection. The AAV-6 with two identical AAV-2 ITRs or two identical AAV-1 ITRs should be the dominant variants. The AAV-6 with two AAV-1 ITRs has been observed by Russell's group [Rutledge, cited above (1998)]. So far there is no report
5 on AAV-6 with two AAV-2 ITRs. Acquisition of AAV-2 P5 promoter by AAV-6 may have explained that AAV-6 have been isolated from human origin while AAV-1 with the same virion has not. The regulation of P5 promoter between different species of AAV may be different *in vivo*. This observation suggests the capsid proteins of AAV were not the only determinants for tissue specificity.

10 Although it is clear that AAV-6 is a hybrid of AAV-1 and AAV-2, AAV-6 has already exhibited divergence from either AAV-1 or AAV-2. There are two nucleotide differences between AAV-6 and AAV-2 in their first 450 nucleotides. There are about 1% differences between AAV-6 and AAV-1 in nucleotide levels from nucleotides 522 to the 3' end. There also exists a quite divergent region (nucleotide
15 4486-4593) between AAV-6 and AAV-1 (Figs. 1A-1C). This region does not encode any known proteins for AAVs. These differences in nucleotide sequences may suggest that AAV-6 and AAV-1 have gone through some evolution since the recombination took place. Another possible explanation is that there exists another variant of AAV-1 which has yet to be identified. So far, there is no evidence to rule
20 out either possibility. It is still unknown if other hybrids (AAV-2 to AAV-4, etc.) existed in nature.

The coding region of AAV-1 was deduced by comparison with other known AAV serotypes. Table 1 illustrates the coding region differences between AAV-1 and AAV-6. The amino acid residues are deduced according to AAV-2.

25 With reference to the amino acid position of AAV-1, Table 1 lists the amino acids of AAV-1 which have been changed to the corresponding ones of AAV-6. The amino acids of AAV-1 are shown to the left of the arrow. Reference may be made to SEQ ID NO: 5 of the amino acid sequence of AAV-1 Rep 78 and to SEQ ID NO: 13 for the amino acid sequence of AAV-1 VP1.

Table 1

Coding region variations between AAV-1 and AAV-6

Rep protein (Rep78)			Cap protein (VP1)	
Position(s)	Amino acids		Position(s)	Amino acids
28	S-N		129	L-F
191	Q-H		418	E-D
192	H-D		531	E-K
308	E-D		584	F-L
			598	A-V
			642	N-H

5 It was surprising to see that the sequence of the AAV-1 coding region is
 10 almost identical to that of AAV-6 from position 452 to the end of coding region
 (99%). The first 508 nucleotides of AAV-6 have been shown to be identical to those
 of AAV-2 [Rutledge, cited above (1998)]. Since the components of AAV-6 genome
 seemed to be AAV-2 left ITR – AAV-2 p5 promoter – AAV-1 coding region – AAV-1
right ITR, it was concluded that AAV-6 is a naturally occurred hybrid between
 15 AAV-1 and AAV-2.

Example 4 - Gene Therapy Vector Based on AAV-1

Recombinant gene transfer vectors based on AAV-1 viruses were constructed
 by the methods described in Example 1. To produce a hybrid recombinant virus with
 AAV-1 virion and AAV-2 ITR, the AAV-1 trans plasmid (pAV1H) and the AAV-2
 20 cis-lacZ plasmid (with AAV-2 ITR) were used. The AAV-2 ITR was used in this
 vector in view of its known ability to direct site-specific integration. Also constructed
 for use in this experiment was an AAV-1 vector carrying the green fluorescent protein
 (GFP) marker gene under the control of the immediate early promoter of CMV using
 pAV1H as the trans plasmid.

A. rAAV-1 Viruses Transfect Host Cells in Vitro

84-31 cells, which are subclones of 293 cells (which express adenovirus E1a, E1b) which stably express E4/ORF5, were infected with rAAV-1 GFP or rAAV-lacZ. High levels of expression of GFP and lacZ was detected in the
5 cultured 84-31 cells. This suggested that rAAV-1 based vector was very similar to AAV-2 based vectors in ability to infect and expression levels.

B. rAAV-1 Viruses Transfect Cells in Vivo

The performance of AAV-1 based vectors was also tested *in vivo*. The rAAV-1 CMV- α 1AT virus was constructed as follows. The EcoRI fragment of
10 pAT85 (ATCC) containing human α 1-antitrypsin (α 1AT) cDNA fragment was blunted and cloned into PCR (Promega) at a SmaI site to obtain PCR- α 1AT. The CMV promoter was cloned into PCR- α 1AT at the XbaI site. The Alb- α 1AT expression cassette was removed by XhoI and ClaI and cloned into pAV1H at the XbaI site. This vector plasmid was used to generate AAV-1-CMV- α 1AT virus used
15 in the experiment described below.

For screening human antibodies against AAV, purified AAV virus is lysed with Ripa buffer (10 mM Tris pH 8.2, 1% Triton X-100, 1% SDS, 0.15 M NaCl) and separated in 10% SDS-PAGE gel. The heat inactivated human serum was used at a 1 to 1000 dilution in this assay. The rAAV-1 CMV- α 1AT viruses were
20 injected into Rag-1 mice through tail vein injection at different dosages. The concentration of human α 1-antitrypsin in mouse serum was measured using ELISA. The coating antibody is rabbit anti-human human α 1-antitrypsin (Sigma). The goat-antihuman α 1-antitrypsin (Sigma) was used as the primary detection antibodies. The sensitivity of this assay is around 0.3 ng/ml to 30 ng/ml. The expression of human α -
25 antitrypsin in mouse blood can be detected in a very encouraging level. This result is shown in Table 2.

Table 2

Human Antitrypsin Expressed in Mouse Liver

Amount of virus injected	Week 2 (ng/ml)	Week 4 (ng/ml)
2x10 ¹⁰ genomes	214.2	171.4
1x10 ¹⁰ genomes	117.8	109.8
5x10 ¹⁰ genomes	64.5	67.8
2.5x10 ¹⁰ genomes	30.9	58.4

5
10
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rAAV-1 CMV-lacZ viruses were also injected into the muscle of C57BL6 mice and similar results were obtained. Collectively, these results suggested that AAV-1 based vector would be appropriate for both liver and muscle gene delivery.

Example 5 - Neutralizing Antibodies Against AAV-1

Simple and quantitative assays for neutralizing antibodies (NAB) to AAV-1 and AAV-2 were developed with recombinant vectors. A total of 33 rhesus monkeys and 77 normal human subjects were screened.

A. Nonhuman Primates

Wild-caught juvenile rhesus monkeys were purchased from Covance (Alice, Tex.) and LABS of Virginia (Yemassee, SC) and kept in full quarantine. The monkeys weighed approximately 3 to 4 kg. The nonhuman primates used in the Institute for Human Gene Therapy research program are purposefully bred in the United States from specific-pathogen-free closed colonies. All vendors are US Department of Agriculture class A dealers. The rhesus macaques are therefore not infected with important simian pathogens, including the tuberculosis agent, major simian lentiviruses (simian immunodeficiency virus and simian retroviruses), and cercopithecine herpesvirus. The animals are also free of internal and external parasites. The excellent health status of these premium animals minimized the potential for extraneous variables. For this study, serum was obtained from monkeys prior to initiation of any protocol.

NAB titers were analyzed by assessing the ability of serum antibody to inhibit the transduction of reporter virus expressing green fluorescent protein (GFP) (AAV1-GFP or AAV2-GFP) into 84-31 cells. Various dilutions of antibodies preincubated with reporter virus for 1 hour at 37°C were added to 90% confluent cell
5 cultures. Cells were incubated for 48 hours and the expression of green fluorescent protein was measured by FluoroImaging (Molecular Dynamics). NAB titers were calculated as the highest dilution at which 50% of the cells stained green.

Analysis of NAB in rhesus monkeys showed that 61% of animals tested positive for AAV-1; a minority (24%) has NAB to AAV-2. Over one-third of
10 animals had antibodies to AAV-1 but not AAV-2 (i.e., were monospecific for AAV-1), whereas no animals were positive for AAV-2 without reacting to AAV-1. These data support the hypothesis that AAV-1 is endemic in rhesus monkeys. The presence of true AAV-2 infections in this group of nonhuman primates is less clear, since cross-neutralizing activity of an AAV-1 response to AAV-2 can not be ruled out. It is
15 interesting that there is a linear relationship between AAV-2 NAB and AAV-1 NAB in animals that had both.

B. *Humans*

For these neutralization antibody assays, human serum samples were incubated at 56°C for 30 min to inactivate complement and then diluted in DMEM.
20 The virus (rAAV or rAd with either lacZ or GFP) was then mixed with each serum dilution (20X, 400X, 2000X, 4000X, etc.) and incubated for 1 hour at 37°C before applied to 90% confluent cultures of 84-31 cells (for AAV) or Hela cells (for adenovirus) in 96-well plates. After 60 minutes of incubation at culture condition, 100 µl additional media containing 20% FCS was added to make final culture media
25 containing 10% FCS.

The result is summarized in Table 3.

Table 3

Adenovirus	AAV-1	AAV-2	# of samples	Percentage
-	-	-	41	53.2%
+	-	-	16	20.8%
-	+	-	0	0.0%
-	-	+	2	2.6%
-	+	+	2	2.6%
+	-	+	3	3.9%
+	+	-	0	0.0%
+	+	+	13	16.9%
Total			77	100%

The human neutralizing antibodies against these three viruses seemed to be unrelated since the existence of neutralizing antibodies against AAV are not indications for antibodies against adenovirus. However, AAV requires adenovirus as helper virus, in most of the cases, the neutralizing antibodies against AAV correlated with the existence of neutralizing antibodies to adenovirus. Among the 77 human serum samples screened, 41% of the samples can neutralize the infectivity of recombinant adenovirus based on Ad5. 15/77 (19%) of serum samples can neutralize the transduction of rAAV-1 while 20/77 (20%) of the samples inhibit rAAV-2 transduction at 1 to 80 dilutions or higher. All serum samples positive in neutralizing antibodies for AAV-1 in are also positive for AAV-2. However, there are five (6%) rAAV-2 positive samples that failed to neutralize rAAV-1. In samples that are positive for neutralizing antibodies, the titer of antibodies also varied in the positive ones. The results from screening human sera for antibodies against AAVs supported the conclusion that AAV-1 presents the same epitome as that of AAV-2 to interact

with cellular receptors since AAV-1 neutralizing human serums can also decrease the infectivity of AAV-2. However, the profile of neutralizing antibodies for these AAVs is not identical, there are additional specific receptors for each AAV serotype.

Example 6 - Recombinant AAV Viruses Exhibit Tissue Tropism

- 5 The recombinant AAV-1 vectors of the invention and the recombinant AAV-2 vectors [containing the gene encoding human α 1-antitrypsin (α 1AT) or murine erythropoietin (Epo) from a cytomegalovirus-enhanced β -actin promoter (CB)] were evaluated in a direct comparison to equivalent copies of AAV-2 vectors containing the same vector genes.
- 10 Recombinant viruses with AAV-1 capsids were constructed using the techniques in Example 1. To make rAAV with AAV-1 virions, pAV1H or p5E18 (2/1) was used as the *trans* plasmid to provide Rep and Cap functions. For the generation of the rAAV based on AAV-2, p5E18(2/2) was used as the *trans* plasmid, since it greatly improved the rAAV yield. [Early experiments indicated similar *in vivo*
- 15 performances of AAV-1 vectors produced with pAV1H and p5E19 (2/1). All subsequent studies used AAV-1 vectors derived from p5E18(2/1) because of the increased yield.]
- 20 Equivalent stocks of the AAV-1 and AAV-2 vectors were injected intramuscularly (5×10^{10} genomes) or liver via the portal circulation (1×10^{11} genomes) into immunodeficient mice, and the animals (four groups) were analyzed on day 30 for expression of transgene. See, Figs. 4A and 4B.
- 25 AAV-2 vectors consistently produced 10- to 50-fold more serum erythropoietin or α 1-antitrypsin when injected into liver compared to muscle. (However, the AAV-1-delivered genes did achieve acceptable expression levels in the liver.) This result was very different from that for AAV-1 vectors, with which muscle expression was equivalent to or greater than liver expression. In fact, AAV-1 outperformed AAV-2 in muscle when equivalent titers based on genomes were administered.

Example 7 - Gene Delivery via rAAV-1

C57BL/6 mice (6- to 8-week old males, Jackson Laboratories) were analyzed for AAV mediated gene transfer to liver following intrasplenic injection of vector (i.e., targeted to liver). A total of 10^{11} genome equivalents of rAAV-1 or rAAV-2 vector
5 were injected into the circulation in 100 μ l buffered saline. The first vector contained either an AAV-1 capsid or an AAV-2 capsid and expressed α 1AT under the control of the chicken β -actin (CB) promoter. Day 28 sera were analyzed for antibodies against AAV-1 or AAV-2 and serum α 1AT levels were checked. Animals were then injected with an AAV-1 or AAV-2 construct expressing erythropoietin (Epo, also under the
10 control of the CB promoter). One month later sera was analyzed for serum levels of Epo. The following groups were analyzed (Figs. 5A-5D).

In Group 1, vector 1 was AAV-2 expressing α 1AT and vector 2 was AAV-2 expressing Epo. Animals generated antibodies against AAV-2 following the first vector administration which prevented the readministration of the AAV-2 based
15 vector. There was no evidence for cross-neutralizing the antibody to AAV-1.

In Group 2, vector 1 was AAV-1 expressing α 1AT while vector 2 was AAV-1 expressing Epo. The first vector administration did result in significant α 1AT expression at one month associated with antibodies to neutralizing antibodies to AAV-1. The animals were not successfully readministered with the AAV-1 Epo
20 expressing construct.

In Group 3, the effectiveness of an AAV-2 vector expressing Epo injected into a naive animal was measured. The animals were injected with PBS and injected with AAV-2 Epo vector at day 28 and analyzed for Epo expression one month later. The neutralizing antibodies were evaluated at day 28 so we did not expect to see anything
25 since they received PBS with the first vector injection. This shows that in naive animals AAV-2 is very efficient at transferring the Epo gene as demonstrated by high level of serum Epo one month later.

Group 4 was an experiment similar to Group 3 in which the animals originally received PBS for vector 1 and then the AAV-1 expressing Epo construct 28 days
30 later. At the time of vector injection, there obviously were no antibodies to either

AAV-1 or AAV-2. The AAV-1 based vector was capable of generating significant expression of Epo when measured one month later.

Group 5 is a cross-over experiment where the initial vector is AAV-2 expressing α 1AT followed by the AAV-1 construct expressing Epo. The animals, as expected, were efficiently infected with the AAV-2 vector expressing α 1AT as shown by high levels of the protein in blood at 28 days. This was associated with significant neutralizing antibodies to AAV-2. Importantly, the animals were successfully administered AAV-1 following the AAV-2 vector as shown by the presence of Epo in serum 28 days following the second vector administration. At the time of this vector administration, there was high level AAV-2 neutralizing antibodies and very low cross-reaction to AAV-1. The level of Epo was slightly diminished possibly due to a small amount of cross-reactivity. Group 6 was the opposite cross-over experiment in which the initial vector was AAV-1 based, whereas the second experiment was AAV-2 based. The AAV-1 vector did lead to significant gene expression of α 1AT, which also resulted in high level AAV-1 neutralizing antibody. The animals were very efficiently administered AAV-2 following the initial AAV-1 vector as evidenced by high level Epo.

A substantially identical experiment was performed in muscle in which 5×10^{10} genomes were injected into the tibialis anterior of C57BL/6 mice as a model for muscle directed gene therapy. The results are illustrated in Figs. 6A-6D and are essentially the same as for liver.

In summary, this experiment demonstrates the utility of using an AAV-1 vector in patients who have pre-existing antibodies to AAV-2 or who had initially received an AAV-2 vector and need readministration.

25 Example 8 - Construction of Recombinant Viruses Containing AAV-1 ITRs

This example illustrates the construction of recombinant AAV vectors which contain AAV-1 ITRs of the invention.

An AAV-1 cis plasmid is constructed as follows. A 160 bp Xho-NruI AAV-1 fragment containing the AAV-1 5' ITR is obtained from pAV1-BL. pAV1-BL was

generated as described in Example 1. The Xho-NruI fragment is then cloned into a second pAV1-BL plasmid at an XbaI site to provide the plasmid with two AAV-1 ITRs. The desired transgene is then cloned into the modified pAV-1BL at the NruI and BamHI site, which is located between the AAV-1 ITR sequences. The resulting
5 AAV-1 cis plasmid contains AAV-1 ITRs flanking the transgene and lacks functional AAV-1 rep and cap.

Recombinant AAV is produced by simultaneously transfecting three plasmids into 293 cells. These include the AAV-1 cis plasmid described above; a trans plasmid which provides AAV rep/cap functions and lacks AAV ITRs; and a plasmid providing
10 adenovirus helper functions. The rep and/or cap functions may be provided in trans by AAV-1 or another AAV serotype, depending on the immunity profile of the intended recipient. Alternatively, the rep or cap functions may be provided in cis by AAV-1 or another serotype, again depending on the patient's immunity profile.

In a typical cotransfection, 50 µg of DNA (cis:trans:helper at ratios of 1:1:2,
15 respectively) is transfected onto a 15 cm tissue culture dish. Cells are harvested 96 hours post transfection, sonicated and treated with 0.5% sodium deoxycholate (37° for 10 min). Cell lysates are then subjected to 2-3 rounds of ultracentrifugation in a cesium gradient. Peak fractions containing rAAV are collected, pooled and dialyzed against PBS. A typical yield is 1×10^{13} genomes/ 10^9 cells.

20 Using this method, one recombinant virus construct is prepared which contains the AAV-1 ITRs flanking the transgene, with an AAV-1 capsid. Another recombinant virus construct is prepared with contains the AAV-1 ITRs flanking the transgene, with an AAV-2 capsid.

All publications cited in this specification are incorporated herein by reference.
25 While the invention has been described with reference to a particularly preferred embodiments, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the claims.

What is claimed is:

1. An isolated AAV-1 nucleic acid molecule comprising a sequence selected from the group consisting of:
 - (a) SEQ ID NO: 1;
 - (b) a DNA sequence complementary to SEQ ID NO: 1;
 - (c) cDNA complementary to (a) or (b); and
 - (d) RNA complementary to any of (a) to (c).
2. A nucleic acid molecule comprising an AAV-1 inverted terminal repeat (ITR) sequence selected from the group consisting of:
 - (a) nt 1 to 143 of SEQ ID NO: 1;
 - (b) nt 4576 to 4718 of SEQ ID NO: 1;
 - (c) a nucleic acid sequence complementary to (a) or (b); and
 - (d) a functional fragment of (a), (b), or (c).
3. A recombinant vector comprising a 5' AAV-1 inverted terminal repeat (ITR) and a selected transgene, wherein said ITR has the sequence selected from the group consisting of:
 - (a) nt 1 to 143 of SEQ ID NO: 1;
 - (b) a nucleic acid sequence complementary to (a); and
 - (c) a functional fragment of (a) or (b).
4. The recombinant vector according to claim 3, wherein said vector further comprises a 3' AAV-1 ITR.

5. A recombinant vector comprising a 3' AAV-1 inverted terminal repeat (ITR) and a selected transgene, wherein said ITR has the sequence selected from the group consisting of:

- (a) nt 4576 to 4718 of SEQ ID NO: 1;
- (b) a nucleic acid sequence complementary to (a); and
- (c) a functional fragment of (a) or (b).

6. The recombinant vector according to claim 5, wherein said vector further comprises a 5' AAV-1 ITR.

7. The recombinant vector according to any of claims 3-6, wherein said vector further comprises AAV-1 capsid proteins having the sequence of SEQ ID NO: 13, 15 or 17 or functional fragments thereof.

8. The recombinant vector according to any of claims 3-6, wherein said vector further comprises adenovirus sequences.

9. A recombinant vector comprising an AAV-1 P5 promoter having the sequence of nt 236 to 299 of SEQ ID NO: 1 or a functional fragment thereof.

10. A nucleic acid molecule encoding AAV-1 helper functions, said molecule comprising an AAV rep coding region and an AAV cap coding region, wherein said cap coding region comprises at least one member is selected from the group consisting of:

- (a) vp1, nt 2223 to 4431 of SEQ ID NO: 1;
- (b) vp2, nt 2634 to 4432 of SEQ ID NO: 1; and
- (c) vp3, nt 2829 to 4432 of SEQ ID NO: 1.

11. A nucleic acid molecule encoding AAV-1 helper functions, said molecule comprising an AAV rep coding region and an AAV cap coding region, wherein said rep coding region comprises an AAV-1 rep coding region comprising at least one member selected from the group consisting of:

- (a) rep 78, nt 335 to 2304 of SEQ ID NO: 1;
- (b) rep 68, nt 335 to 2272 of SEQ ID NO: 1 or the cDNA corresponding thereto;
- (c) rep 52, nt 1007 to 2304 of SEQ ID NO: 1; and
- (d) rep 40, nt 1007 to 2272 of SEQ ID NO: 1 or the cDNA corresponding thereto.

12. A host cell transduced with a recombinant viral vector according to any of claims 3-6.

13. A host cell transduced with a nucleic acid molecule according to any of claims 1, 2, 10 or 11.

14. A host cell stably transduced with an AAV-1 P5 promoter having the sequence of nt 236 to 299 of SEQ ID NO: 1.

15. A pharmaceutical composition comprising a carrier and a virus comprising the vector according to any of claims 3-6.

16. A pharmaceutical composition comprising a carrier and a virus comprising the vector according to claim 7.

17. A pharmaceutical composition comprising a carrier and a virus comprising the vector according to claim 8.

18. A method for AAV-mediated delivery of a transgene comprising the step of delivering to a host cell an AAV virion which comprises:

- (a) a capsid comprising at least one capsid protein encoded by an AAV-1 cap gene; and
- (b) a DNA molecule comprising a transgene under the control of regulatory sequences directing its expression.

19. A method for AAV-mediated delivery of a transgene to a host comprising the steps of:

- (a) assaying a sample from the host to determine the presence of neutralizing antibodies specific against any serotype of AAV; and
- (b) delivering to the host an AAV virion which comprises:
 - (i) a capsid comprising at least one capsid protein encoded by a cap gene of an AAV serotype against which the host has no antibodies as determined in step (a); and
 - (ii) a DNA molecule comprising a transgene under the control of regulatory sequences directing its expression.

20. The method according to claim 19, comprising the additional step of repeating steps (a) and (b).

21. Use of an AAV virion which comprises a capsid comprising (a) at least one capsid protein encoded by a cap gene of an AAV serotype against which the host has antibodies, and (b) a DNA molecule comprising a transgene operably linked to regulatory sequences directing its expression,

in the preparation of a medicament for delivery of a transgene to a host, wherein said host has no preexisting neutralizing antibodies against the AAV serotype of said cap gene.

22. A method for delivery of a transgene comprising the step of delivering to a host cell a recombinant virus comprising a recombinant vector according to any of claims 3-8.

23. A method for producing a selected gene product comprising the steps of transfecting a mammalian cell with the molecule according to claim 1 or a functional fragment thereof and culturing said cell under conditions suitable to express said gene product.

[illegible]

[illegible]

FIG 2

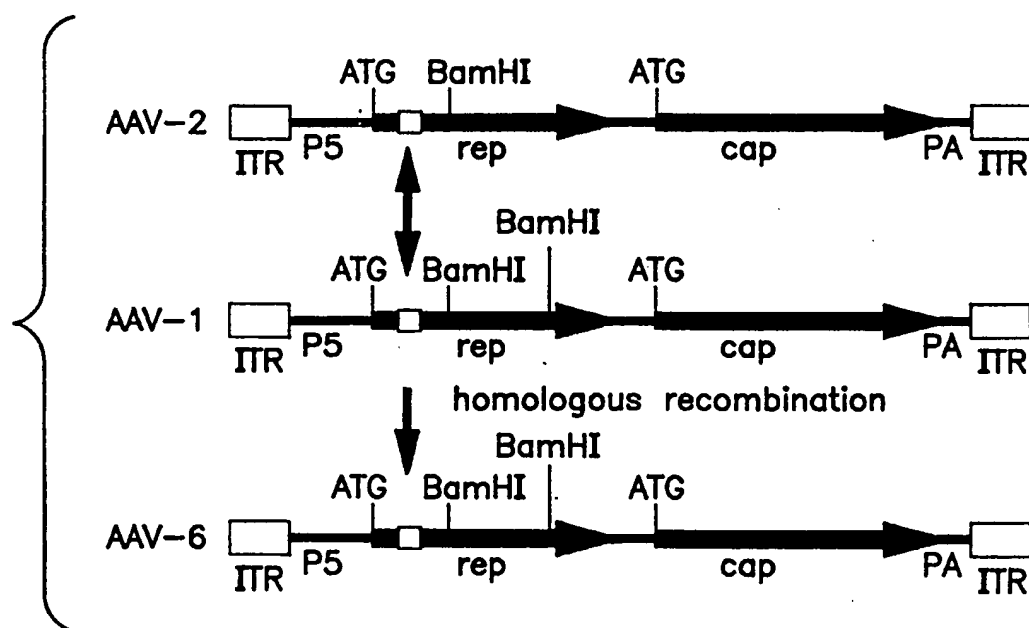


FIG. 3A

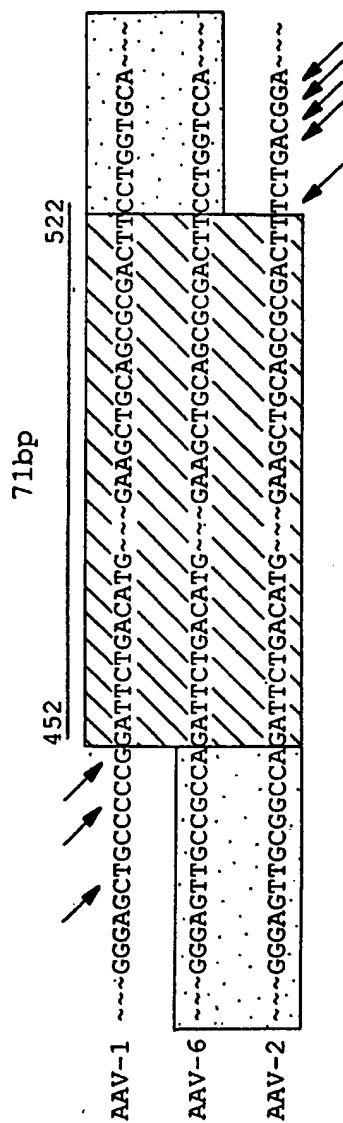


FIG. 3B

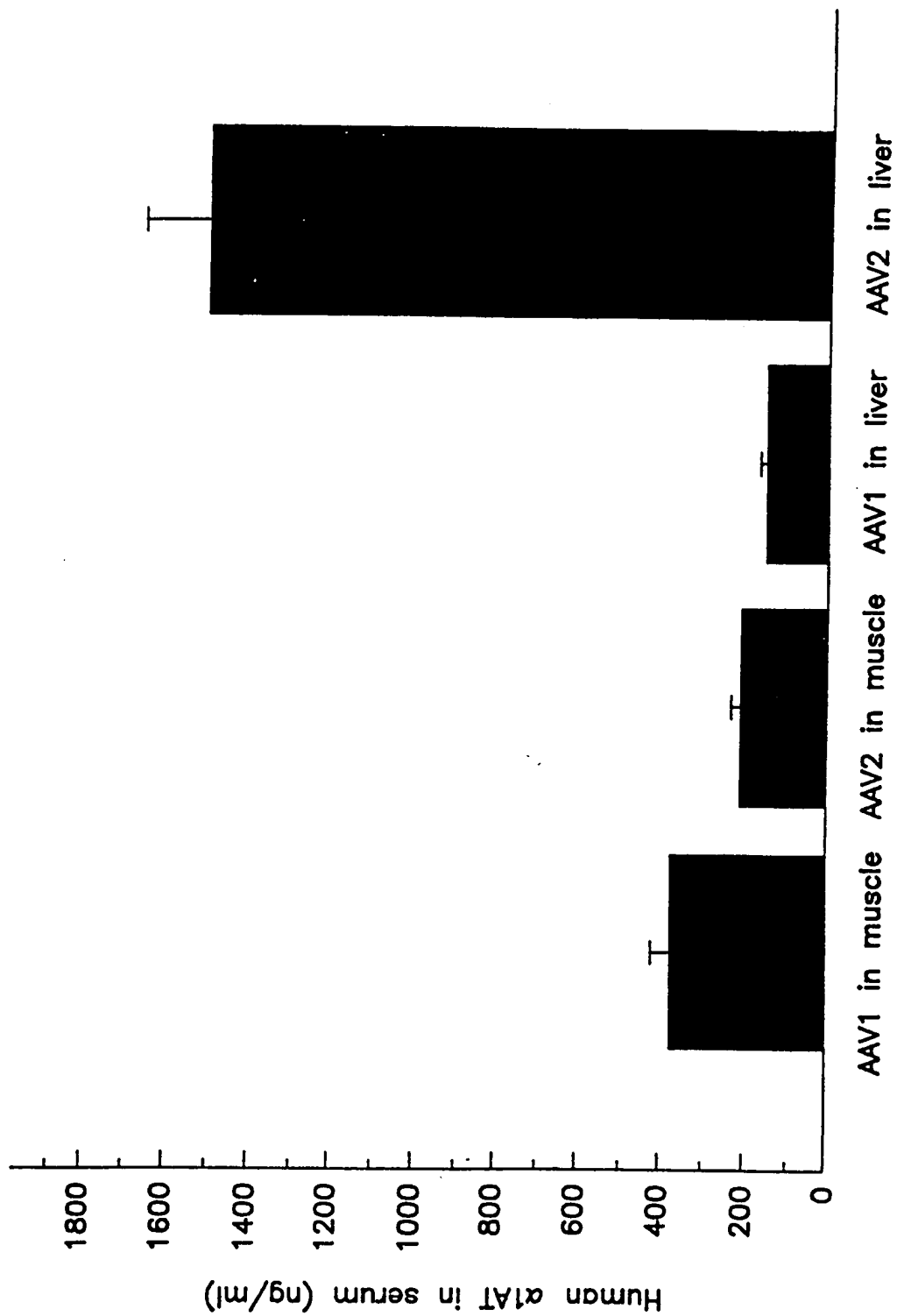


FIG. 4A

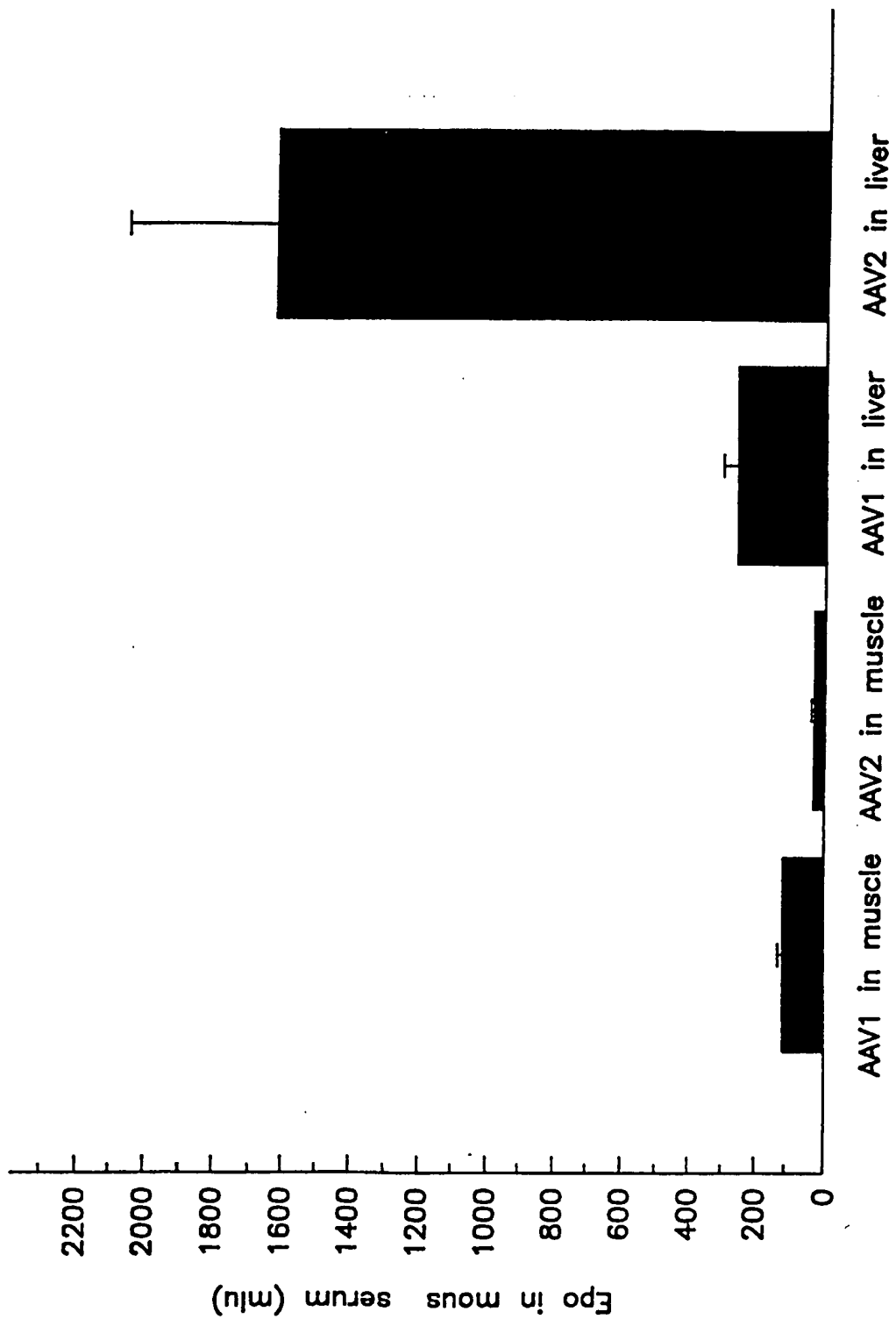


FIG. 4B

FIG. 5A

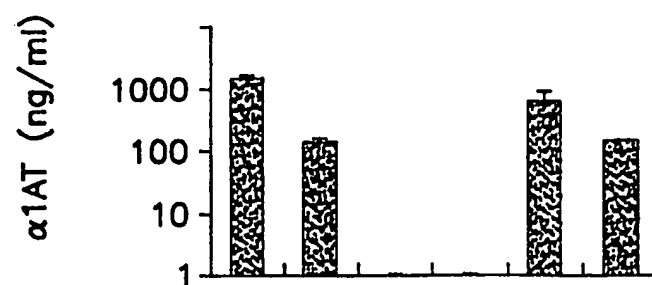


FIG. 5B

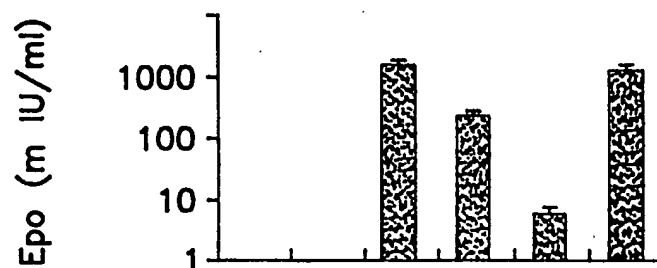


FIG. 5C

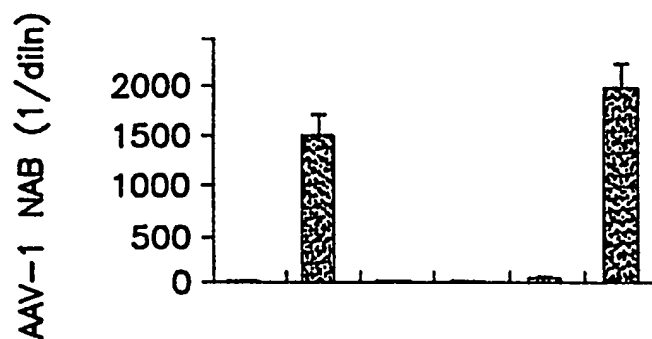
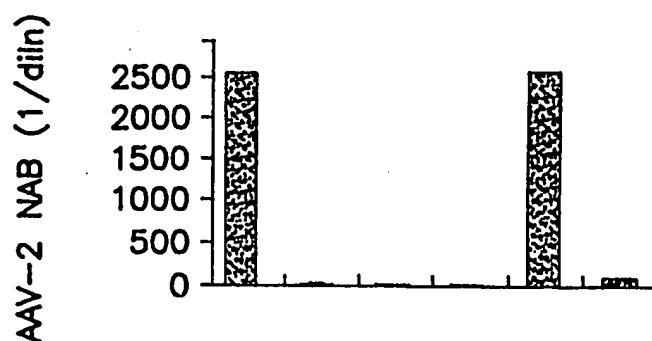


FIG. 5D



Group	1	2	3	4	5	6
Vector1-α1AT	AAV2	AAV1	PBS	PBS	AAV2	AAV1
Vector2-EPO	AAV2	AAV1	AAV2	AAV1	AAV1	AAV2

FIG. 6A

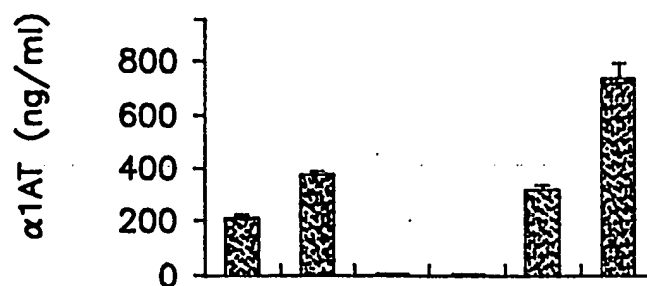


FIG. 6B

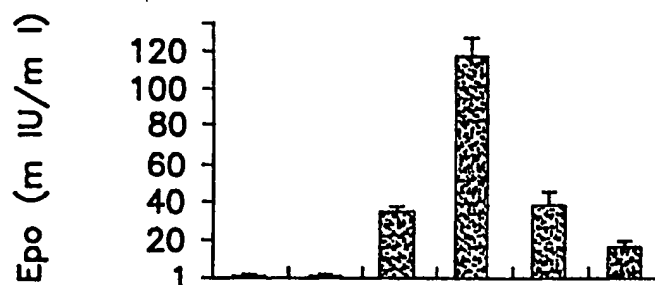


FIG. 6C

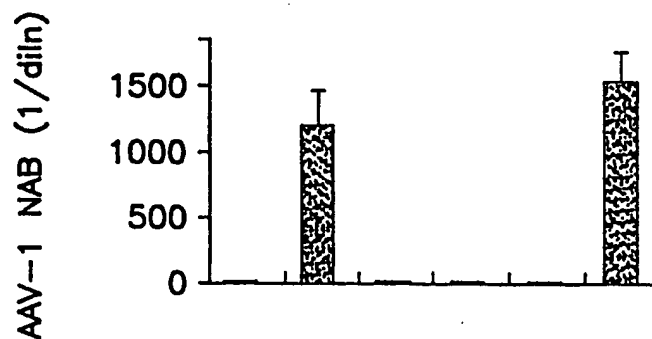
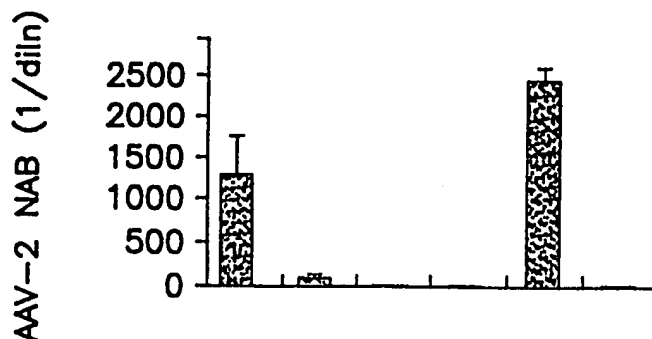


FIG. 6D



Group	1	2	3	4	5	6
Vector1- α 1AT	AAV2	AAV1	PBS	PBS	AAV2	AAV1
V ctor2-EPO	AAV2	AAV1	AAV2	AAV1	AAV1	AAV2

SEQUENCE LISTING

<110> Wilson, James M.

Xiao, Weidong

The Trustees of the University of Pennsylvania

<120> Adeno-Associated Virus Serotype I Nucleic Acid
Sequences, Vectors and Host Cells Containing Same

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Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr Gly Asp Ser	
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Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro Ala Thr Pro	
805 810 815	
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Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly Ala Pro Met	
820 825 830 835	
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Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala Ser Gly Asn	
840 845 850	
tgg cat tgc gat tcc aca tgg ctg ggc gac aga gtc atc acc acc agc	2951
Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile Thr Thr Ser	
855 860 865	
acc cgc acc tgg gcc ttg ccc acc tac aat aac cac ctc tac aag caa	2999
Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu Tyr Lys Gln	
870 875 880	
atc tcc agt gct tca acg ggg gcc agc aac gac aac cac tac ttc ggc	3047
Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His Tyr Phe Gly	
885 890 895	
tac agc acc ccc tgg ggg tat ttt gat ttc aac aga ttc cac tgc cac	3095
Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe His Cys His	
900 905 910 915	
ttt tca cca cgt gac tgg cag cga ctc atc aac aac aat tgg gga ttc	3143
Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn Trp Gly Phe	
920 925 930	
cgg ccc aag aga ctc aac ttc aaa ctc ttc aac atc caa gtc aag gag	3191
Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln Val Lys Glu	
935 940 945	
gtc acg acg aat gat ggc gtc aca acc atc gct aat aac ctt acc agc	3239
Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn Leu Thr Ser	
950 955 960	

acg gtt caa gtc ttc tcg gac tcg gag tac cag ctt ccg tac gtc ctc	3287
Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro Tyr Val Leu	
965 970 975	
ggc tct gcg cac cag ggc tgc ctc cct ccg ttc ccg gcg gac gtg ttc	3335
Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala Asp Val Phe	
980 985 990 995	
atg att ccg caa tac ggc tac ctg acg ctc aac aat ggc agc caa gcc	3383
Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly Ser Gln Ala	
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gtg gga cgt tca tcc ttt tac tgc ctg gaa tat ttc cct tct cag atg	3431
Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro Ser Gln Met	
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Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe Glu Glu Val	
1030 1035 1040	
cct ttc cac agc agc tac gcg cac agc cag agc ctg gac cgg ctg atg	3527
Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met	
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Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Asn Arg Thr Gln Asn	
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Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser Arg Gly Ser	
1080 1085 1090	
cca gct ggc atg tct gtt cag ccc aaa aac tgg cta cct gga ccc tgt	3671
Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro Gly Pro Cys	
1095 1100 1105	
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Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn Asn Asn Ser	
1110 1115 1120	
aat ttt acc tgg act ggt gct tca aaa tat aac ctc aat ggg cgt gaa	3767
Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn Gly Arg Glu	
1125 1130 1135	
tcc atc atc aac cct ggc act gct atg gcc tca cac aaa gac gac gaa	3815
Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys Asp Asp Glu	
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gac aag ttc ttt ccc atg agc ggt gtc atg att ttt gga aaa gag agc	3863
Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe Gly Lys Glu Ser	
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gcc gga gct tca aac act gca ttg gac aat gtc atg att aca gac gaa	3911
Ala Gly Ala Ser Asn Thr Ala Leu Asp Asn Val Met Ile Thr Asp Glu	
1175 1180 1185	
gag gaa att aaa gcc act aac cct gtg gcc acc gaa aga ttt ggg acc	3959
Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg Phe Gly Thr	
1190 1195 1200	
gtg gca gtc aat ttc cag agc agc agc aca gac cct gcg acc gga gat	4007
Val Ala Val Asn Phe Gln Ser Ser Ser Thr Asp Pro Ala Thr Gly Asp	
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Val His Ala Met Gly Ala Leu Pro Gly Met Val Trp Gln Asp Arg Asp	
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gtg tac ctg cag ggt ccc att tgg gcc aaa att cct cac aca gat gga	4103
Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly	
1240 1245 1250	
cac ttt cac ccg tct cct ctt atg ggc ggc ttt gga ctc aag aac ccg	4151
His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu Lys Asn Pro	
1255 1260 1265	
cct cct cag atc ctc atc aaa aac acg cct gtt cct gcg aat cct ccg	4199
Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala Asn Pro Pro	
1270 1275 1280	
gcg gag ttt tca gct aca aag ttt gct tca ttc atc acc caa tac tcc	4247
Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr Gln Tyr Ser	
1285 1290 1295	
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Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln Lys Glu Asn	
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agc aag cgc tgg aat ccc gaa gtg cag tac aca tcc aat tat gca aaa	4343
Ser Lys Arg Trp Asn Pro Glu Val Gln Tyr Thr Ser Asn Tyr Ala Lys	
1320 1325 1330	
tct gcc aac gtt gat ttt act gtg gac aac aat gga ctt tat act gag	4391
Ser Ala Asn Val Asp Phe Thr Val Asp Asn Asn Gly Leu Tyr Thr Glu	
1335 1340 1345	

cct cgc ccc att ggc acc cgt tac ctt acc cgt ccc ctg taattacgtg 4440
 Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Pro Leu
 1350 1355 1360

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 35 40 45

 Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
 50 55 60

 Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
 65 70 75 80

 Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu
 85 90 95

 Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
 100 105 110

 Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu
 115 120 125

 Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly
 130 135 140

Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys
 145 150 155 160

Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile
 165 170 175

Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His
 180 185 190

Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn
 195 200 205

Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr
 210 215 220

Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
 225 230 235 240

Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 245 250 255

Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
 260 265 270

Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
 275 280 285

Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
 290 295 300

Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
 305 310 315 320

Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
 325 330 335

Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
 340 345 350

Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
 355 360 365

Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
 370 375 380

Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
 385 390 395 400

Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
 405 410 415
 Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
 420 425 430
 Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
 435 440 445
 Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
 450 455 460
 Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
 465 470 475 480
 Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
 485 490 495
 Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
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 Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
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 Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met
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 Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile
 545 550 555 560
 Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val
 565 570 575
 Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys
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 35 40 45
 Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
 50 55 60
 Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
 65 70 75 80
 Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
 85 90 95
 Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
 100 105 110
 Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
 115 120 125
 Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
 130 135 140
 Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly
 145 150 155 160
 Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
 165 170 175
 Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro
 180 185 190
 Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
 195 200 205
 Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala
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 Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile
 225 230 235 240
 Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu

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Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His					
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Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe					
	275		280		285
His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn					
	290		295		300
Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln					
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					320
Val Lys Glu Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn					
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Leu Thr Ser Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro					
	340		345		350
Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala					
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Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly					
	370		375		380
Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro					
	385		390		395
					400
Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe					
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Glu Glu Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp					
	420		425		430
Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Asn Arg					
	435		440		445
Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser					
	450		455		460
Arg Gly Ser Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro					
	465		470		475
					480
Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn					
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Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn					

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Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys		
515	520	525
Asp Asp Glu Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe Gly		
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Lys Glu Ser Ala Gly Ala Ser Asn Thr Ala Leu Asp Asn Val Met Ile		
545	550	555
Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg		
565	570	575
Phe Gly Thr Val Ala Val Asn Phe Gln Ser Ser Ser Thr Asp Pro Ala		
580	585	590
Thr Gly Asp Val His Ala Met Gly Ala Leu Pro Gly Met Val Trp Gln		
595	600	605
Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His		
610	615	620
Thr Asp Gly His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu		
625	630	635
Lys Asn Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala		
645	650	655
Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr		
660	665	670
Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln		
675	680	685
Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Val Gln Tyr Thr Ser Asn		
690	695	700
Tyr Ala Lys Ser Ala Asn Val Asp Phe Thr Val Asp Asn Asn Gly Leu		
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Tyr Thr Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Pro Leu		
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Glu His Leu Pro Gly Ile Ser Asp Ser Phe Val Ser Trp Val Ala Glu	
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Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile	
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 gag cag gca ccc ctg acc gtg gcc gag aag ctg cag cgc gac ttc ctg	192
Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu	
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 gtc caa tgg cgc cgc gtg agt aag gcc ccg gag gcc ctc ttc ttt gtt	240
Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val	
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 cag ttc gag aag ggc gag tcc tac ttc cac ctc cat att ctg gtg gag	288
Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu	
85 90 95	
 acc acg ggg gtc aaa tcc atg gtg ctg gcc cgc ttc ctg agt cag att	336
Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile	
100 105 110	
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Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu	
115 120 125	
 ccc aac tgg ttc gcg gtg acc aag acg cgt aat ggc gcc gga ggg ggg	432
Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly	
130 135 140	
 aac aag gtg gtg gac gag tgc tac atc ccc aac tac ctc ctg ccc aag	480
Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys	
145 150 155 160	
 act cag ccc gag ctg cag tgg gcg tgg act aac atg gag gag tat ata	528

Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile	
165 170 175	
agc gcc tgt ttg aac ctg gcc gag cgc aaa cgg ctc gtg gcg cag cac	576
Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His	
180 185 190	
ctg acc cac gtc agc cag acc cag gag cag aac aag gag aat ctg aac	624
Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn	
195 200 205	
ccc aat tct gac gcg cct gtc atc cgg tca aaa acc tcc gcg cgc tac	672
Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr	
210 215 220	
atg gag ctg gtc ggg tgg ctg gtg gac cgg ggc atc acc tcc gag aag	720
Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys	
225 230 235 240	
cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct	768
Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala	
245 250 255	
tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag	816
Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys	
260 265 270	
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Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala	
275 280 285	
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Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu	
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Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala	
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Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala	
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Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro	
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Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp	
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Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val	
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Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser	
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ccc gat gac gcg gat aaa agc gag ccc aag cgg gcc tgc ccc tca gtc	1536
Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val	
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Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala	
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Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met	
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Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile
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 565 570 575

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 Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys
 580 585 590

 gcc att cat cat ctg ctg ggg cgg gct ccc gag att gct tgc tgc gcc 1824
 Ala Ile His His Leu Leu Gly Arg Ala Pro Glu Ile Ala Cys Ser Ala
 595 600 605

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 35 40 45

 Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
 50 55 60

 Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
 65 70 75 80

 Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu
 85 90 95

 Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
 100 105 110

 Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu

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Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys		
145	150	155
Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile		
	165	170
		175
Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His		
	180	185
		190
Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn		
	195	200
		205
Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr		
	210	215
		220
Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys		
	225	230
		235
		240
Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala		
	245	250
		255
Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys		
	260	265
		270
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala		
	275	280
		285
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu		
	290	295
		300
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala		
	305	310
		315
		320
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala		
	325	330
		335
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro		
	340	345
		350
Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp		
	355	360
		365
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala		

370	375	380
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg		
385	390	395 400
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val		
	405	410 415
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser		
	420	425 430
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe		
	435	440 445
Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln		
	450	455 460
Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val		
	465	470 475 480
Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala		
	485	490 495
Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val		
	500	505 510
Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala		
	515	520 525
Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met		
	530	535 540
Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile		
	545	550 555 560
Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val		
	565	570 575
Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys		
	580	585 590
Ala Ile His His Leu Leu Gly Arg Ala Pro Glu Ile Ala Cys Ser Ala		
	595	600 605
Cys Asp Leu Val Asn Val Asp Leu Asp Asp Cys Val Ser Glu Gln		
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<220>

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<222> (1)..(1638)

<400> 6

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Met Pro Gly Phe Tyr Glu Ile Val Ile Lys Val Pro Ser Asp Leu Asp
   1             5             10             15

gag cac ctg ccg ggc att tct gac tcg ttt gtg agc tgg gtg gcc gag      96
Glu His Leu Pro Gly Ile Ser Asp Ser Phe Val Ser Trp Val Ala Glu
          20             25             30

aag gaa tgg gag ctg ccc ccg gat tct gac atg gat ctg aat ctg att     144
Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile
          35             40             45

gag cag gca ccc ctg acc gtg gcc gag aag ctg cag cgc gac ttc ctg     192
Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
          50             55             60

gtc caa tgg cgc cgc gtg agt aag gcc ccg gag gcc ctc ttc ttt gtt     240
Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
          65             70             75             80

cag ttc gag aag ggc gag tcc tac ttc cac ctc cat att ctg gtg gag     288
Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu
          85             90             95

acc acg ggg gtc aaa tcc atg gtg ctg ggc cgc ttc ctg agt cag att     336
Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
          100            105            110

agg gac aag ctg gtg cag acc atc tac cgc ggg atc gag ccg acc ctg     384
Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu
          115            120            125

ccc aac tgg ttc gcg gtg acc aag acg cgt aat ggc gcc gga ggg ggg     432
Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly
          130            135            140

aac aag gtg gtg gac gag tgc tac atc ccc aac tac ctc ctg ccc aag     480
Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys

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145	150	155	160	
act cag ccc gag ctg cag tgg gcg tgg act aac atg gag gag tat ata				528
Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile				
	165	170	175	
agc gcc tgt ttg aac ctg gcc gag cgc aaa cgg ctc gtg gcg cag cac				576
Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His				
	180	185	190	
ctg acc cac gtc agc cag acc cag gag cag aac aag gag aat ctg aac				624
Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn				
	195	200	205	
ccc aat tct gac gcg cct gtc atc cgg tca aaa acc tcc gcg cgc tac				672
Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr				
	210	215	220	
atg gag ctg gtc ggg tgg ctg gtg gac cgg ggc atc acc tcc gag aag				720
Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys				
	225	230	235	240
cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct				768
Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala				
	245	250	255	
tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag				816
Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys				
	260	265	270	
atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct				864
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala				
	275	280	285	
ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg				912
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu				
	290	295	300	
aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc				960
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala				
	305	310	315	320
cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccg gcc				1008
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala				
	325	330	335	
acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc				1056
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro				

340	345	350	
ttc tac ggc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat			1104
Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp			
355	360	365	
tgc gtc gac aag atg gtg atc tgg tgg gag gag ggc aag atg acg gcc			1152
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala			
370	375	380	
aag gtc gtg gag tcc gcc aag gcc att ctc ggc ggc agc aag gtg cgc			1200
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg			
385	390	395 400	
gtg gac caa aag tgc aag tcg tcc gcc cag atc gac ccc acc ccc gtg			1248
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val			
405	410	415	
atc gtc acc tcc aac acc aac atg tgc gcc gtg att gac ggg aac agc			1296
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser			
420	425	430	
acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt			1344
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe			
435	440	445	
gaa ctc acc cgc cgt ctg gag cat gac ttt ggc aag gtg aca aag cag			1392
Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln			
450	455	460	
gaa gtc aaa gag ttc ttc cgc tgg gcg cag gat cac gtg acc gag gtg			1440
Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val			
465	470	475 480	
gcg cat gag ttc tac gtc aga aag ggt gga gcc aac aaa aga ccc gcc			1488
Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala			
485	490	495	
ccc gat gac gcg gat aaa agc gag ccc aag cgg gcc tgc ccc tca gtc			1536
Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val			
500	505	510	
gcg gat cca tcg acg tca gac gcg gaa gga gct ccg gtg gac ttt gcc			1584
Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala			
515	520	525	
gac agg tat ggc tgc cga tgg tta tct tcc aga ttg gct cga gga caa			1632
Asp Arg Tyr Gly Cys Arg Trp Leu Ser Ser Arg Leu Ala Arg Gly Gln			

530

535

540

cct ctc tga

1641

Pro Leu

545

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<211> 546

<212> PRT

<213> AAV-1

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 20 25 30

Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile
 35 40 45

Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
 50 55 60

Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
 65 70 75 80

Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu
 85 90 95

Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
 100 105 110

Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu
 115 120 125

Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly
 130 135 140

Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys
 145 150 155 160

Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile
 165 170 175

Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His
 180 185 190

Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn
 195 200 205

Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr
 210 215 220

Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
 225 230 235 240

Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 245 250 255

Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
 260 265 270

Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
 275 280 285

Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
 290 295 300

Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
 305 310 315 320

Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
 325 330 335

Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
 340 345 350

Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
 355 360 365

Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
 370 375 380

Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
 385 390 395 400

Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
 405 410 415

Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
 420 425 430

Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
 435 440 445

Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
 450 455 460

Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
 465 470 475 480

Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
 485 490 495

Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
 500 505 510

Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
 515 520 525

Asp Arg Tyr Gly Cys Arg Trp Leu Ser Ser Arg Leu Ala Arg Gly Gln
 530 535 540

Pro Leu
 545

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 cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct 96
 Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 20 25 30
 tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag 144
 Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
 35 40 45
 atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct 192
 Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
 50 55 60

ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg	240
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu	
65 70 75 80	
aac gcc tac gaa cct gcc tac gcc gcc tcc gtc ttt ctc gcc tgg gcc	288
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala	
85 90 95	
cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccg gcc	336
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala	
100 105 110	
acc acg gcc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc	384
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro	
115 120 125	
ttc tac gcc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat	432
Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp	
130 135 140	
tgc gtc gac aag atg gtg atc tgg tgg gag gag gcc aag atg acg gcc	480
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala	
145 150 155 160	
aag gtc gtg gag tcc gcc aag gcc att ctc gcc gcc agc aag gtg cgc	528
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg	
165 170 175	
gtg gac caa aag tgc aag tcg tcc gcc cag atc gac ccc acc ccc gtg	576
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val	
180 185 190	
atc gtc acc tcc aac acc aac atg tgc gcc gtg att gac ggg aac agc	624
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser	
195 200 205	
acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt	672
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe	
210 215 220	
gaa ctc acc cgc cgt ctg gag cat gac ttt gcc aag gtg aca aag cag	720
Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln	
225 230 235 240	
gaa gtc aaa gag ttc ttc cgc tgg gcg cag gat cac gtg acc gag gtg	768
Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val	
245 250 255	

gcg cat gag ttc tac gtc aga aag ggt gga gcc aac aaa aga ccc gcc 816
 Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
 260 265 270

ccc gat gac gcg gat aaa agc gag ccc aag cgg gcc tgc ccc tca gtc 864
 Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
 275 280 285

gcg gat cca tcg acg tca gac gcg gaa gga gct ccg gtg gac ttt gcc 912
 Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
 290 295 300

gac agg tac caa aac aaa tgt tct cgt cac gcg ggc atg ctt cag atg 960
 Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met
 305 310 315 320

ctg ttt ccc tgc aag aca tgc gag aga atg aat cag aat ttc aac att 1008
 Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile
 325 330 335

tgc ttc acg cac ggg acg aga gac tgt tca gag tgc ttc ccc ggc gtg 1056
 Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val
 340 345 350

tca gaa tct caa ccg gtc gtc aga aag agg acg tat cgg aaa ctc tgt 1104
 Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys
 355 360 365

gcc att cat cat ctg ctg ggg cgg gct ccc gag att gct tgc tcg gcc 1152
 Ala Ile His His Leu Leu Gly Arg Ala Pro Glu Ile Ala Cys Ser Ala
 370 375 380

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 385 390 395

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<212> PRT

<213> AAV-1

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Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala

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Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys	35	40	45		
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala	50	55	60		
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu	65	70	75	80	
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala	85	90	95		
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala	100	105	110		
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro	115	120	125		
Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp	130	135	140		
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala	145	150	155	160	
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg	165	170	175		
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val	180	185	190		
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser	195	200	205		
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe	210	215	220		
Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln	225	230	235	240	
Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val	245	250	255		
Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala	260	265	270		
Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val					

275 280 285
 Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
 290 295 300
 Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met
 305 310 315 320
 Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile
 325 330 335
 Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val
 340 345 350
 Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys
 355 360 365
 Ala Ile His His Leu Leu Gly Arg Ala Pro Glu Ile Ala Cys Ser Ala
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 Cys Asp Leu Val Asn Val Asp Leu Asp Asp Cys Val Ser Glu Gln
 385 390 395

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<211> 969

<212> DNA

<213> AAV-1

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<221> misc_feature

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<223> minor splice site

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 cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct 96
 Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 20 25 30
 tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag 144


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Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
      35              40              45

atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct   192
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
      50              55              60

ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg   240
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
      65              70              75              80

aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc   288
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
      85              90              95

cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccg gcc   336
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
      100             105             110

acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc   384
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
      115             120             125

ttc tac ggc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat   432
Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
      130             135             140

tgc gtc gac aag atg gtg atc tgg tgg gag gag ggc aag atg acg gcc   480
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
      145             150             155             160

aag gtc gtg gag tcc gcc aag gcc att ctc ggc ggc agc aag gtg cgc   528
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
      165             170             175

gtg gac caa aag tgc aag tcg tcc gcc cag atc gac ccc acc ccc gtg   576
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
      180             185             190

atc gtc acc tcc aac acc aac atg tgc gcc gtg att gac ggg aac agc   624
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
      195             200             205

acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt   672
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
      210             215             220

gaa ctc acc cgc cgt ctg gag cat gac ttt ggc aag gtg aca aag cag   720

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Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
 225 230 235 240

 gaa gtc aaa gag ttc ttc cgc tgg gcg cag gat cac gtg acc gag gtg 768
 Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
 245 250 255

 gcg cat gag ttc tac gtc aga aag ggt gga gcc aac aaa aga ccc gcc 816
 Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
 260 265 270

 ccc gat gac gcg gat aaa agc gag ccc aag cgg gcc tgc ccc tca gtc 864
 Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
 275 280 285

 gcg gat cca tcg acg tca gac gcg gaa gga gct ccg gtg gac ttt gcc 912
 Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
 290 295 300

 gac agg tat ggc tgc cga tgg tta tct tcc aga ttg gct cga gga caa 960
 Asp Arg Tyr Gly Cys Arg Trp Leu Ser Ser Arg Leu Ala Arg Gly Gln
 305 310 315 320

 cct ctc tga 969
 Pro Leu

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 <212> PRT
 <213> AAV-1

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 Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 20 25 30

 Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
 35 40 45

 Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
 50 55 60

 Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
 65 70 75 80

Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
 85 90 95

 Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
 100 105 110

 Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
 115 120 125

 Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
 130 135 140

 Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
 145 150 155 160

 Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
 165 170 175

 Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
 180 185 190

 Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
 195 200 205

 Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
 210 215 220

 Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
 225 230 235 240

 Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
 245 250 255

 Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
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 Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
 275 280 285

 Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
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 Pro Leu

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gag ggc att cgc gag tgg tgg gac ttg aaa cct gga gcc ccg aag ccc   96
Glu Gly Ile Arg Glu Trp Trp Asp Leu Lys Pro Gly Ala Pro Lys Pro
           20             25             30

aaa gcc aac cag caa aag cag gac gac ggc cgg ggt ctg gtg ctt cct   144
Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro
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ggc tac aag tac ctc gga ccc ttc aac gga ctc gac aag ggg gag ccc   192
Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
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gtc aac gcg gcg gac gca gcg gcc ctc gag cac gac aag gcc tac gac   240
Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
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cag cag ctc aaa gcg ggt gac aat ccg tac ctg cgg tat aac cac gcc   288
Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
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gac gcc gag ttt cag gag cgt ctg caa gaa gat acg tct ttt ggg ggc   336
Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
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aac ctc ggg cga gca gtc ttc cag gcc aag aag cgg gtt ctc gaa cct   384
Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
           115            120            125

ctc ggt ctg gtt gag gaa ggc gct aag acg gct cct gga aag aaa cgt   432
Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
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ccg gta gag cag tcg cca caa gag cca gac tcc tcc tcg ggc atc ggc   480

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Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly
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 ggc gac tca gag tca gtc ccc gat cca caa cct ctc gga gaa cct cca 576
 Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro
 180 185 190

 gca acc ccc gct gct gtg gga cct act aca atg gct tca ggc ggt ggc 624
 Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
 195 200 205

 gca cca atg gca gac aat aac gaa ggc gcc gac gga gtg ggt aat gcc 672
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 Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile
 225 230 235 240

 acc acc agc acc cgc acc tgg gcc ttg ccc acc tac aat aac cac ctc 768
 Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
 245 250 255

 tac aag caa atc tcc agt gct tca acg ggg gcc agc aac gac aac cac 816
 Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His
 260 265 270

 tac ttc ggc tac agc acc ccc tgg ggg tat ttt gat ttc aac aga ttc 864
 Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe
 275 280 285

 cac tgc cac ttt tca cca cgt gac tgg cag cga ctc atc aac aac aat 912
 His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn
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 tgg gga ttc cgg ccc aag aga ctc aac ttc aaa ctc ttc aac atc caa 960
 Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln
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 gtc aag gag gtc acg acg aat gat ggc gtc aca acc atc gct aat aac 1008
 Val Lys Glu Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn
 325 330 335

 ctt acc agc acg gtt caa gtc ttc tcg gac tcg gag tac cag ctt ccg 1056

Leu Thr Ser Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro	
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Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala	
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Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly	
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Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro	
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Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe	
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Glu Glu Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp	
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Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Asn Arg	
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act caa aat cag tcc gga agt gcc caa aac aag gac ttg ctg ttt agc	1392
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Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn	
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Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys	
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Lys	Glu	Ser	Ala	Gly	Ala	Ser	Asn	Thr	Ala	Leu	Asp	Asn	Val	Met	Ile		
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Thr	Asp	Glu	Glu	Glu	Ile	Lys	Ala	Thr	Asn	Pro	Val	Ala	Thr	Glu	Arg		
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Phe	Gly	Thr	Val	Ala	Val	Asn	Phe	Gln	Ser	Ser	Ser	Thr	Asp	Pro	Ala		
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Thr	Gly	Asp	Val	His	Ala	Met	Gly	Ala	Leu	Pro	Gly	Met	Val	Trp	Gln		
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gat	aga	gac	gtg	tac	ctg	cag	ggt	ccc	att	tgg	gcc	aaa	att	cct	cac	1872	
Asp	Arg	Asp	Val	Tyr	Leu	Gln	Gly	Pro	Ile	Trp	Ala	Lys	Ile	Pro	His		
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Thr	Asp	Gly	His	Phe	His	Pro	Ser	Pro	Leu	Met	Gly	Gly	Phe	Gly	Leu		
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Lys	Asn	Pro	Pro	Pro	Gln	Ile	Leu	Ile	Lys	Asn	Thr	Pro	Val	Pro	Ala		
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aat	cct	ccg	gcg	gag	ttt	tca	gct	aca	aag	ttt	gct	tca	ttc	atc	acc	2016	
Asn	Pro	Pro	Ala	Glu	Phe	Ser	Ala	Thr	Lys	Phe	Ala	Ser	Phe	Ile	Thr		
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Gln	Tyr	Ser	Thr	Gly	Gln	Val	Ser	Val	Glu	Ile	Glu	Trp	Glu	Leu	Gln		
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Lys	Glu	Asn	Ser	Lys	Arg	Trp	Asn	Pro	Glu	Val	Gln	Tyr	Thr	Ser	Asn		
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tat	gca	aaa	tct	gcc	aac	gtt	gat	ttt	act	gtg	gac	aac	aat	gga	ctt	2160	
Tyr	Ala	Lys	Ser	Ala	Asn	Val	Asp	Phe	Thr	Val	Asp	Asn	Asn	Gly	Leu		
705					710					715				720			
tat	act	gag	cct	cgc	ccc	att	ggc	acc	cgt	tac	ctt	acc	cgt	ccc	ctg	2208	

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2211

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 35 40 45

Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
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Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
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Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
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Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
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Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
 115 120 125

Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
 130 135 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly
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Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
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Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro
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Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
 195 200 205

Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala
 210 215 220

Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile
 225 230 235 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
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Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His
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Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe
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His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn
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Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln
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Val Lys Glu Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn
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Leu Thr Ser Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro
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Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala
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Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly
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Glu Glu Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp
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Arg Gly Ser Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro
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Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn
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Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn
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Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys
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Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg
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Phe Gly Thr Val Ala Val Asn Phe Gln Ser Ser Ser Thr Asp Pro Ala
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Thr Gly Asp Val His Ala Met Gly Ala Leu Pro Gly Met Val Trp Gln
 595 600 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
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Thr Asp Gly His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu
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Lys Asn Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
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Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr
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Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
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Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Val Gln Tyr Thr Ser Asn
 690 695 700

Tyr Ala Lys Ser Ala Asn Val Asp Phe Thr Val Asp Asn Asn Gly Leu
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 Asp Ser Ser Ser Gly Ile Gly Lys Thr Gly Gln Gln Pro Ala Lys Lys
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aga ctc aat ttt ggt cag act ggc gac tca gag tca gtc ccc gat cca 144
 Arg Leu Asn Phe Gly Gln Thr Gly Asp Ser Glu Ser Val Pro Asp Pro
 35 40 45

caa cct ctc gga gaa cct cca gca acc ccc gct gct gtg gga cct act 192
 Gln Pro Leu Gly Glu Pro Pro Ala Thr Pro Ala Ala Val Gly Pro Thr
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aca atg gct tca ggc ggt ggc gca cca atg gca gac aat aac gaa ggc 240
 Thr Met Ala Ser Gly Gly Gly Ala Pro Met Ala Asp Asn Asn Glu Gly
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gcc gac gga gtg ggt aat gcc tca gga aat tgg cat tgc gat tcc aca 288
 Ala Asp Gly Val Gly Asn Ala Ser Gly Asn Trp His Cys Asp Ser Thr
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tgg ctg ggc gac aga gtc atc acc acc agc acc cgc acc tgg gcc ttg 336
 Trp Leu Gly Asp Arg Val Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu
 100 105 110

ccc acc tac aat aac cac ctc tac aag caa atc tcc agt gct tca acg 384
 Pro Thr Tyr Asn Asn His Leu Tyr Lys Gln Ile Ser Ser Ala Ser Thr
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Gly Ala Ser Asn Asp Asn His Tyr Phe Gly Tyr Ser Thr Pro Trp Gly
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Tyr Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp
145 150 155 160

cag cga ctc atc aac aac aat tgg gga ttc cgg ccc aag aga ctc aac 528
Gln Arg Leu Ile Asn Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn
165 170 175

ttc aaa ctc ttc aac atc caa gtc aag gag gtc acg acg aat gat ggc 576
Phe Lys Leu Phe Asn Ile Gln Val Lys Glu Val Thr Thr Asn Asp Gly
180 185 190

gtc aca acc atc gct aat aac ctt acc agc acg gtt caa gtc ttc tcg 624
Val Thr Thr Ile Ala Asn Asn Leu Thr Ser Thr Val Gln Val Phe Ser
195 200 205

gac tcg gag tac cag ctt ccg tac gtc ctc ggc tct gcg cac cag ggc 672
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210 215 220

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Cys Leu Pro Pro Phe Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly
225 230 235 240

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Tyr Leu Thr Leu Asn Asn Gly Ser Gln Ala Val Gly Arg Ser Ser Phe
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Tyr Cys Leu Glu Tyr Phe Pro Ser Gln Met Leu Arg Thr Gly Asn Asn
260 265 270

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Phe Thr Phe Ser Tyr Thr Phe Glu Glu Val Pro Phe His Ser Ser Tyr
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gcg cac agc cag agc ctg gac cgg ctg atg aat cct ctc atc gac caa 912
Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln
290 295 300

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Tyr Leu Tyr Tyr Leu Asn Arg Thr Gln Asn Gln Ser Gly Ser Ala Gln
305 310 315 320

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Ala Leu Asp Asn Val Met Ile Thr Asp Glu Glu Glu Ile Lys Ala Thr	
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Ser Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Ala Met Gly Ala	
450 455 460	
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Ile Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro	
485 490 495	
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Leu Met Gly Gly Phe Gly Leu Lys Asn Pro Pro Pro Gln Ile Leu Ile	
500 505 510	

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 Lys Asn Thr Pro Val Pro Ala Asn Pro Pro Ala Glu Phe Ser Ala Thr
 515 520 525

aag ttt gct tca ttc atc acc caa tac tcc aca gga caa gtg agt gtg 1632
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gaa att gaa tgg gag ctg cag aaa gaa aac agc aag cgc tgg aat ccc 1680
 Glu Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro
 545 550 555 560

gaa gtg cag tac aca tcc aat tat gca aaa tct gcc aac gtt gat ttt 1728
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 565 570 575

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Gln Pro Leu Gly Glu Pro Pro Ala Thr Pro Ala Ala Val Gly Pro Thr
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Thr Met Ala Ser Gly Gly Gly Ala Pro Met Ala Asp Asn Asn Glu Gly
 65 70 75 80

Ala Asp Gly Val Gly Asn Ala Ser Gly Asn Trp His Cys Asp Ser Thr

	85		90		95
Trp Leu Gly Asp Arg Val Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu					
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Pro Thr Tyr Asn Asn His Leu Tyr Lys Gln Ile Ser Ser Ala Ser Thr					
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Gly Ala Ser Asn Asp Asn His Tyr Phe Gly Tyr Ser Thr Pro Trp Gly					
	130		135		140
Tyr Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp					
145		150		155	160
Gln Arg Leu Ile Asn Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn					
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Phe Lys Leu Phe Asn Ile Gln Val Lys Glu Val Thr Thr Asn Asp Gly					
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Val Thr Thr Ile Ala Asn Asn Leu Thr Ser Thr Val Gln Val Phe Ser					
	195		200		205
Asp Ser Glu Tyr Gln Leu Pro Tyr Val Leu Gly Ser Ala His Gln Gly					
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Cys Leu Pro Pro Phe Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly					
225		230		235	240
Tyr Leu Thr Leu Asn Asn Gly Ser Gln Ala Val Gly Arg Ser Ser Phe					
	245		250		255
Tyr Cys Leu Glu Tyr Phe Pro Ser Gln Met Leu Arg Thr Gly Asn Asn					
	260		265		270
Phe Thr Phe Ser Tyr Thr Phe Glu Glu Val Pro Phe His Ser Ser Tyr					
	275		280		285
Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln					
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Tyr Leu Tyr Tyr Leu Asn Arg Thr Gln Asn Gln Ser Gly Ser Ala Gln					
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Asn Lys Asp Leu Leu Phe Ser Arg Gly Ser Pro Ala Gly Met Ser Val					
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Gln Pro Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val					

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Ser Lys Thr Lys Thr Asp Asn Asn Asn Ser Asn Phe Thr Trp Thr Gly		
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Ala Ser Lys Tyr Asn Leu Asn Gly Arg Glu Ser Ile Ile Asn Pro Gly		
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Thr Ala Met Ala Ser His Lys Asp Asp Glu Asp Lys Phe Phe Pro Met		
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Ser Gly Val Met Ile Phe Gly Lys Glu Ser Ala Gly Ala Ser Asn Thr		
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Ala Leu Asp Asn Val Met Ile Thr Asp Glu Glu Glu Ile Lys Ala Thr		
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Asn Pro Val Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Phe Gln		
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Ser Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Ala Met Gly Ala		
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Leu Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro		
465	470	475
Ile Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro		
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Leu Met Gly Gly Phe Gly Leu Lys Asn Pro Pro Pro Gln Ile Leu Ile		
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Lys Asn Thr Pro Val Pro Ala Asn Pro Pro Ala Glu Phe Ser Ala Thr		
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Lys Phe Ala Ser Phe Ile Thr Gln Tyr Ser Thr Gly Gln Val Ser Val		
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Glu Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro		
545	550	555
Glu Val Gln Tyr Thr Ser Asn Tyr Ala Lys Ser Ala Asn Val Asp Phe		
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Asp Gly Val Gly Asn Ala Ser Gly Asn Trp His Cys Asp Ser Thr Trp
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ctg ggc gac aga gtc atc acc acc agc acc cgc acc tgg gcc ttg ccc 144
Leu Gly Asp Arg Val Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro
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acc tac aat aac cac ctc tac aag caa atc tcc agt gct tca acg ggg 192
Thr Tyr Asn Asn His Leu Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly
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gcc agc aac gac aac cac tac ttc ggc tac agc acc ccc tgg ggg tat 240
Ala Ser Asn Asp Asn His Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr
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Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp Gln
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cga ctc atc aac aac aat tgg gga ttc cgg ccc aag aga ctc aac ttc 336
Arg Leu Ile Asn Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe
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aaa ctc ttc aac atc caa gtc aag gag gtc acg acg aat gat ggc gtc 384
Lys Leu Phe Asn Ile Gln Val Lys Glu Val Thr Thr Asn Asp Gly Val
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aca acc atc gct aat aac ctt acc agc acg gtt caa gtc ttc tcg gac 432
Thr Thr Ile Ala Asn Asn Leu Thr Ser Thr Val Gln Val Phe Ser Asp
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Cys Leu Glu Tyr Phe Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe	
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Thr Phe Ser Tyr Thr Phe Glu Glu Val Pro Phe His Ser Ser Tyr Ala	
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Lys Asp Leu Leu Phe Ser Arg Gly Ser Pro Ala Gly Met Ser Val Gln	
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Pro Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser	
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 Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile
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1605

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Ala Ser Asn Asp Asn His Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr
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Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp Gln
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Arg Leu Ile Asn Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe
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Lys Leu Phe Asn Ile Gln Val Lys Glu Val Thr Thr Asn Asp Gly Val
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Thr Thr Ile Ala Asn Asn Leu Thr Ser Thr Val Gln Val Phe Ser Asp
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Ser Glu Tyr Gln Leu Pro Tyr Val Leu Gly Ser Ala His Gln Gly Cys
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 His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr
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<213> rep binding motif

<400> 20

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16

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 15/86, 15/35, 5/10, A61K 48/00	A3	(11) International Publication Number: WO 00/28061 (43) International Publication Date: 18 May 2000 (18.05.00)
(21) International Application Number: PCT/US99/25694 (22) International Filing Date: 2 November 1999 (02.11.99) (30) Priority Data: 60/107,114 5 November 1998 (05.11.98) US (71) Applicant (for all designated States except US): THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA [US/US]; Suite 300, 3700 Market Street, Philadelphia, PA 19104-3147 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): WILSON, James, M. [US/US]; 1350 N. Avignon Drive, Gladwyne, PA 19035 (US). XIAO, Weidong [CN/US]; Apartment P4, 155 Washington Lane, Jenkintown, PA 19046 (US). (74) Agents: KODROFF, Cathy, A. et al.; Howson & Howson, Spring House Corporate Center, P.O. Box 457, Spring House, PA 19477 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 3 August 2000 (03.08.00)
(54) Title: ADENO-ASSOCIATED VIRUS SEROTYPE 1 NUCLEIC ACID SEQUENCES, VECTORS AND HOST CELLS CONTAINING SAME (57) Abstract The nucleic acid sequences of adeno-associated virus (AAV) serotype 1 are provided, as are vectors and host cells containing these sequences and functional fragments thereof. Also provided are methods of delivering genes via AAV-1 derived vectors.		

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INTERNATIONAL SEARCH REPORT

Int. J. Application No

PCT/US 99/25694

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12N15/86 C12N15/35 C12N5/10 A61K48/00				
According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12N A61K				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the International search (name of data base and, where practical, search terms used)				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
Y	RUTLEDGE E. A. ET AL.: "Infectious clones and vectors derived from adeno-associated virus (AAV) serotypes other than AAV type 2." JOURNAL OF VIROLOGY, vol. 72, no. 1, January 1998 (1998-01), pages 309-319, XP002137089 ISSN: 0022-538X cited in the application the whole document	1-23		
Y	WO 98 11244 A (SAFER BRIAN ;US HEALTH (US); CHIORINI JOHN A (US); KOTIN ROBERT M) 19 March 1998 (1998-03-19) the whole document	1-23		
-/-				
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.				
<input checked="" type="checkbox"/> Patent family members are listed in annex.				
* Special categories of cited documents : <table border="0"> <tr> <td style="vertical-align: top;"> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the International filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the International filing date but later than the priority date claimed </td> <td style="vertical-align: top;"> "T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family </td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the International filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the International filing date but later than the priority date claimed	"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the International filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the International filing date but later than the priority date claimed	"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family			
Date of the actual completion of the International search 8 May 2000		Date of mailing of the International search report 22/05/2000		
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Mandl, B		

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/25694

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>XIAO W. ET AL.: "Gene therapy vectors based on adeno-associated virus type 1." JOURNAL OF VIROLOGY, vol. 73, no. 5, May 1999 (1999-05), pages 3994-4003, XP002137090 ISSN: 0022-538X the whole document</p>	1-23

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 25694

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 18-20 and 22, as far as an in vivo application is concerned, are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/25694

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9811244 A	19-03-1998	AU 4645697 A EP 0932694 A	02-04-1998 04-08-1999